

**IN THE UNITED STATES DISTRICT COURT  
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA  
CHARLESTON DIVISION**

<b>IN RE: ETHICON, INC. PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LIGATION</b>	<b>Master File No. 2:12-MD-02327 MDL No. 2327</b>
<b>THIS DOCUMENT RELATES TO ALL PLAINTIFFS LISTED IN EXHIBIT “A”</b>	<b>JOSEPH R. GOODWIN U.S. DISTRICT JUDGE</b>

**PLAINTIFFS’ MOTION TO EXCLUDE CERTAIN OPINIONS  
AND TESTIMONY OF CHRISTINA PRAMUDJL, MD**

Plaintiffs respectfully request that the Court preclude defense expert Christina Pramudji, M.D., from giving opinions on: (1) the adequacy of Defendants’ product warnings and IFUs; (2) whether Defendants’ transvaginal mesh products are defectively designed; (3) the safety and efficacy of Defendants’ products based on her own practice; and (4) whether or not the polypropylene mesh in the mesh products degrades beyond what she has personally observed in her own practice. The basis for Plaintiffs’ motion is more fully set out in the accompanying Memorandum.

Dated: April 21, 2016

Respectfully submitted,

/s/ Thomas P. Cartmell  
 Thomas P. Cartmell, Esq.  
 Jeffrey M. Kuntz, Esq.  
 Wagstaff & Cartmell LLP  
 4740 Grand Avenue, Suite 300  
 Kansas City, MO 64112  
 Telephone: (816) 701-1100  
 Facsimile: (816) 531-2372  
[tcartmell@wcllp.com](mailto:tcartmell@wcllp.com)  
[jkuntz@wcllp.com](mailto:jkuntz@wcllp.com)

/s/ D. Renee Baggett

Bryan F. Aylstock, Esq.

Renee Baggett, Esq.

Aylstock, Witkin, Kreis and Overholtz, PLC

17 East Main Street, Suite 200

Pensacola, Florida 32563

Telephone: (850) 202-1010

Facsimile: (850) 916-7449

[baylstock@awkolaw.com](mailto:baylstock@awkolaw.com)

[rbaggett@awkolaw.com](mailto:rbaggett@awkolaw.com)

*Attorneys for Plaintiffs*

**CERTIFICATE OF SERVICE**

I hereby certify that I filed the foregoing document on April 21, 2016 using the Court's CM-ECF filing system, thereby sending notice of the filing to all counsel of record in this matter.

/s/Thomas P. Cartmell  
**Attorney for Plaintiffs**

## **INDEX OF EXHIBITS**

**Exhibit A:** List of cases on which Dr. Pramudji is designated

**Exhibit B:** Pramudji TVT & TVT-O Expert Report

**Exhibit C:** Gynemesh PS, Prolift & Prosmia Expert Report

**Exhibit D:** Pramudji March 24, 2016 Deposition

**Exhibit E:** Pramudji Sept. 17, 2014 Deposition

**Exhibit F:** Owens Sept. 12, 2012 Deposition

**Exhibit G:** Robinson March 14, 2012 Deposition

**Exhibit H:** O'Bryan May 18, 2012 Deposition

**Exhibit I:** Pramudji April 11, 2014 Deposition

# Exhibit A

**EXHIBIT A - PRAMUDJI**

**THIS DOCUMENT RELATES TO  
PLAINTIFFS:**

*Joy Essman*

*Case No. 2:12-cv-00277*

*Barbara A. Hill*

*Case No. 2:12-cv-00806*

*Paula Kriz*

*Case No. 2:12-cv-00938*

*Brenda Riddell*

*Case No. 2:12-cv-00547*

*Sharon Carpenter*

*Case No. 2:12-cv-00554*

*Mary Jane Olsen*

*Case No. 2:12-cv-00470*

*Virginia White*

*Case No. 2:12-cv-00958*

*Sandra Wolfe*

*Case No. 2:12-cv-00335*

*Marie Smith (f/k/a Banks)*

*Case No. 2:12-cv-01318*

*Sherry Fox*

*Case No. 2:12-cv-00878*

*Lois Durham*

*Case No. 2:12-cv-00760*

*Elizabeth Blynn Wilson*

*Case No. 2:12-cv-01286*

*Daphne Barker*

*Case No. 2:12-cv-00899*

*Wendy Hagans*

*Case No. 2:12-cv-00783*

***Maria Eugenia Quijano***  
***Case No. 2:12-cv-00799***

***Sharon Boggs***  
***Case No. 2:12-cv-00368***

***Robin Bridges***  
***Case No. 2:12-cv-00651***

***Carey Cole***  
***Case No. 2:12-cv-00483***

***Cathy Warlick***  
***Case No. 2:12-cv-00276***

***Donna Amsden***  
***Case No. 2:12-cv-00960***

***Heather Long***  
***Case No. 2:12-cv-01275***

***Penny Rhynhart***  
***Case No. 2:12-cv-01119***

***Nancy Jo Williams***  
***Case No. 2:12-cv-00511***

***Maria Stone***  
***Case No. 2:12-cv-00652***

***Teri Key Shively***  
***Case No. 2:12-cv-00379***

***Charlene Logan Taylor***  
***Case No. 2:12-cv-00376***

***Tina Morrow***  
***Case No. 2:12-cv-00378***

***Carol Jean Dimock***  
***Case No. 2:12-cv-00401***

# Exhibit B

### **EXPERT REPORT OF CHRISTINA PRAMUDJI, M.D.**

The following is a summary of my qualifications and my opinions in this case as of the date of this report. This report is based on the information I have now. To the extent I receive additional information between now and the time of the trial, I may form additional opinions or some of my opinions may be modified.

All of my opinions are held to a reasonable degree of medical and scientific certainty and probability. Below is a summary of my general opinions as set forth in more detail in my report. All of my opinions are based on my education, training, and clinical experience, the medical literature and materials that I have reviewed, my discussions with colleagues, my research and review of the medical records and deposition testimony provided to me in this case, and from the perspective of a board-certified urologist with subspecialty board certification in Pelvic Floor Medicine and Reconstructive Surgery.

- Urinary incontinence, including stress and urge incontinence, are common conditions in women. There are many risk factors for incontinence, and more specifically stress urinary incontinence.
- Incontinence can be very distressing and burdensome to women and can cause adverse effects on women physically, mentally, and socially. Incontinence can adversely affect quality of life and relationships.
- Stress urinary incontinence can be treated with lifestyle changes and behavioral therapy, non-surgical options and surgery. More conservative

efforts to treat incontinence may not be a suitable option for some women and they may not always provide relief. Many women who try more conservative measures will discontinue the therapy.

- Surgery for stress urinary incontinence has been shown to be the most definitive treatment. Surgeries include the Burch colposuspension, native/biologic tissue slings and most often, synthetic slings made of monofilament, large pore polypropylene like that used in TVT and TVT-O. The clinical data shows that the TVT and TVT-O Type 1 macroporous Prolene polypropylene mesh is biocompatible, has a minimal inflammatory response, allows for adequate tissue ingrowth and is not associated with a significantly increased risk of infection over that generally associated with SUI and vaginal surgery, which is consistent with my clinical experience in hundreds of women. The data in women does not support that the TVT and TVT-O mesh is cytotoxic, causes an adverse inflammatory response, sarcoma or cancer, or that the way the edges are cut has any clinically significant effect. The data in women also does not support that the TVT and TVT-O mesh degrades, or that if it did it would have a clinically significant effect, and I have not seen evidence of mesh degradation in my clinical practice.
- The TVT and TVT-O have a positive benefit to risk profile. Overall, the TVT and TVT-O have a better benefit/risk profile than the Burch and native tissue slings. The TVT and TVT-O have great utility to surgeons and their patients. Extensive data exist which supports the TVT and TVT-O and shows that they

are minimally invasive and less invasive than the Burch and native tissue slings. Advantages include shorter operative time/anesthetic need, reduced surgical pain, reduced hospitalization, faster recovery, and reduced complications, including voiding dysfunction. Polypropylene mesh has been used for decades. TVT and TVT-O are safe and effective surgical options for the treatment of SUI.

- The TVT and TVT-O slings have been extensively studied. The TVT and TVT-O slings have been studied in over 100 Randomized Controlled Trials (RCTs) and hundreds of other studies. The TVT and TVT-O have also been extensively used in clinical practice by urologists, gynecologists, and urogynecologists. The TVT and TVT-O are taught to doctors during residency and fellowship because they are recognized as a suitable surgical options to treat stress urinary incontinence.
- The TVT and the TVT-O are the Gold Standard and standard of care for treating stress urinary incontinence. Overall cure and improvement rates are generally in the 80-95% range with significant improvements in symptoms and quality of life. Complications are infrequent and manageable. The rate of mesh exposure is 1-2%, voiding dysfunction and retention is about 1-4%, and complications requiring surgical management occur at a rate of 2-4%. Dyspareunia and pain are also rare (<1%) and occur more often with the Burch and native tissue slings. Thus the risk of surgery due to mesh exposure or erosion, voiding dysfunction and retention, and pain is rare even out to

10-17 years follow up according to high level data. The need for a second revision is very uncommon according to the reliable scientific data. Case reports and case series are of limited value and do not address the incidence of complications or primary and secondary management.

- The TVT and TVT-O have been studied and evaluated by members of the pertinent medical and surgical organizations, such as the American Urologic Association (AUA), Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU), American Urogynecologic Society (AUGS), International Continence Society (ICS), National Institute for Health and Care Excellence (NICE), Society of Gynecologic Surgeons (SGS), International Urogynecological Association (IUGA), and the European Association of Urology (EAU), and are found to be safe and effective and widely recognized as the Gold Standard, standard of care, and first line and suitable surgical option to treat stress urinary incontinence.
- All surgeries to treat stress urinary incontinence have risks. Like the TVT and TVT-O, other SUI surgeries are performed in the pelvis and utilize surgical instruments, like Stamey needles, in the surgical field. Potential risks of operating in this area are well described to surgeons during training, in medical textbooks, and in the medical literature, and are well known risks. The same is true for the tensioning of sutures as well as slings, whether made of synthetic or animal or native tissue, and the potential complications such as voiding dysfunction. Pain, pelvic pain, and dyspareunia can occur with any

SUI surgery and vaginal surgery, are well known and described in the literature, as well as taught to surgeons in their education and training. Dyspareunia and sexual dysfunction that preexists in women can also be cured or improve following TVT or TVT-O placement. Mesh exposure/erosion is the only unique risk when using the TVT and TVT-O and it is uncommon and can be easily treated in the majority of cases. Suture and sling erosion and wound complications can occur with non-TVT/TVT-O SUI surgeries. The TVT and TVT-O are not defective in their design and from my perspective as a surgeon, the risks are adequately described in the IFU and professional education materials.

- Although some of Plaintiffs' experts claims that another material, such as PVDF, Prolene Soft, Vypro or Ultrapro that has been used in hernia and prolapse repair, should be used, they point to no similar breadth and length of clinical data in SUI patients to make such comparisons. Nor have they provided data showing that these meshes would work long term in the design of the TVT or TVT-O, which have long term data. These meshes have not been studied to treat SUI in women like TVT and TVT-O. These claims are without adequate scientific support and merit.

## **I. BACKGROUND, TRAINING AND EXPERIENCE**

I am a board certified urologist, with a subspecialty board certification of Pelvic Floor Medicine and Reconstructive Surgery. I received a Bachelor of Science in Chemical Engineering from Georgia Institute of Technology (Georgia Tech) *cum laude*, which included a Chemical Engineering Internship at the University of London. I received my M.D. degree from the University of Alabama School of Medicine in Birmingham in 1996. I then completed a general surgery and urology residency at Baylor College of Medicine in Houston, Texas, where I received extensive training in pelvic floor medicine and surgery. During this training I performed various surgeries to treat urinary incontinence and other pelvic and urologic conditions and disorders. Since then I have been in private practice for over 12 years and the focus of my practice is female urology and pelvic floor medicine.

I have a vast experience with mid-urethral slings, having performed over 900 sling procedures from various manufacturers and of various approaches. I am very familiar with the Ethicon TVT and TVT-O devices, having been trained in their use and having surgically placed them in hundreds of procedures. I have been a consultant for Ethicon and Boston Scientific in sling development. I also have extensive mesh experience in over 600 cases and have managed mesh complications, as well. I have an interest in bladder and pelvic floor surgery, so when I realized that the majority of my practice involved women with those sorts of problems, I decided to make it the major focus of my practice. A copy of my curriculum vitae, which details my training,

education and experience, is attached as **Exhibit "A"** to this report. A list of my publications is also set forth in my CV.

## **II. CHARGES AND TESTIMONIAL HISTORY**

For my work in this case, I am charging \$600 an hour for time spent reviewing and preparing. I charge \$700 an hour for deposition or court testimony. In the past four years, I have given testimony as an expert in the following: Connie & Kevin Schubert v. Freeman Health System et al., Jasper County Missouri Case No. 10AO-CC00219 (8/27/2013 deposition testimony), Carolyn Lewis v. Johnson & Johnson, et al., Case No.: 2:12-cv-04301 (1/10/2014 deposition testimony), and Huskey/Edwards v. Johnson & Johnson, et al., (4/11/2014 deposition testimony and 9/3-4/2014 trial testimony).

## **III. MATERIALS REVIEWED**

In this case, I have reviewed the medical records and the available deposition transcripts. I have reviewed the expert reports submitted by the plaintiffs, specifically the reports of Drs. Rosenzweig, Margolis and Carey, as well as the materials cited in the reports and their expert depositions.

I have also reviewed the IFU for Ethicon's TVT-O product, the Patient Brochure, as well as the professional education materials used by Ethicon relating to the TVT and TVT-O procedures. Through my training, clinical and surgical experience, professional activities including CME and conference attendance, my lecturing and professional education to other pelvic floor surgeons, and my review of the literature, I am familiar with urinary incontinence, the treatment of incontinence, the TVT and TVT-O, and the

medical literature relating to the development of TVT and TVT-O and their safety and effectiveness. In preparation for my testimony, I have reviewed some of that literature, as set out in **Exhibit "B."** Exhibits that will be used to support my findings and opinions, as well as documents that I have reviewed, are identified above, cited in my report, and listed in **Exhibit "B"** as well. These materials and the examination, in addition to my personal experience, knowledge, training, and education, have informed the opinions referenced above and which follow.

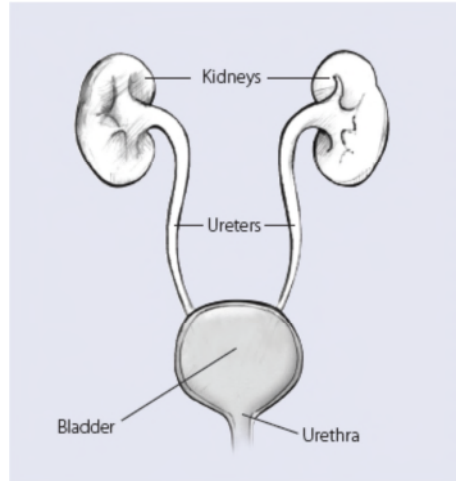
#### **IV. OPINIONS**

My conclusions and opinions are based in the practice of evidence-based medicine. As state above, I hold all opinions set forth in this report to a reasonable degree of medical and scientific certainty and probability.

##### **A. Urinary Incontinence**

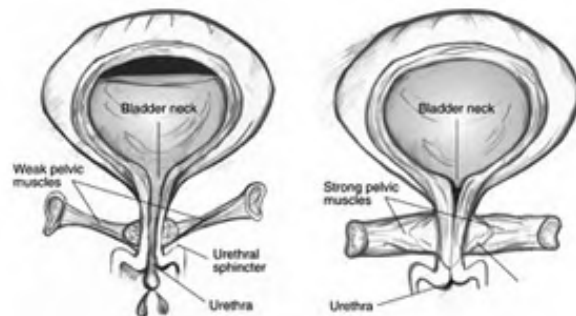
Urinary incontinence is the involuntary leakage of urine and is a common condition in women. Incontinence can be a result of different abnormalities of function of the lower urinary tract or as a result of other illnesses, which tend to cause leakage in different situations. There are different types of incontinence including stress urinary incontinence (SUI), which occurs with exertion, coughing, sneezing, or other activity or movement, and urgency incontinence, which is the involuntary leakage of urine that follows a sudden need to urinate and is caused by the bladder muscles contracting. Women can have either or both of these types of incontinence and when both are present it is termed mixed incontinence.

As can be seen in the diagram, the bladder is the organ in our body that holds urine. Waste is filtered by the kidneys and urine flows down the ureters connecting the bladder. Connected to the bladder is a tube called the urethra. The urethra is at the bottom of the urinary tract and allows urine to be passed from the body.



(AUA Foundation 2013 A Patient's Guide, 1 in 3 Women experience Stress Urinary Incontinence.)

Involuntary leakage of urine with SUI results when intra-abdominal pressure increases and exceeds the ability of the urethra to stay closed.



There are many factors associated with the development of SUI. Risk factors include increasing age, obesity, parity and vaginal delivery, diabetes, hormone replacement therapy, and family history. Other factors, including hysterectomy, physical activity and smoking have been reported to increase the risk of SUI. Caucasian and Hispanics have an increased risk of SUI. Nerve injuries to the lower back and pelvic surgery are also potential risk factors for development of SUI because they weaken the

pelvic floor muscles. (Stress Urinary Incontinence, A Monograph from the AUA Foundation 2011).

Although prevalence of incontinence varies by study cohort and definition, it is common. For example, SUI has been reported to occur in up to 35% of women. A study of the National Health and Nutrition Examination Survey (NHANES) in 4,229 women aged 20 or older showed that 49.6% reported urinary incontinence symptoms, and of those 49.8% reported pure stress incontinence, 34.3% mixed incontinence and 15.9% pure urge incontinence. (Dooley Y, et al. Urinary incontinence prevalence: results from the National Health and Nutrition Examination Survey. J Urol. 2008; 179:656-61.)

Comparative data from NHANES 2007-2008 show an increase in the prevalence of UI in women to 53.4%, which was partially explained by differences in age, race/ethnicity, obesity, diabetes and select chronic diseases. (Markland AD, et al. Prevalence and trends of urinary incontinence in adults in the United States, 2001 to 2008. J Urol. 2011; 186:589-93).

In another NHANES survey of nonpregnant women, the prevalence of SUI increased as women got older. There the authors focused on moderate or severe urinary incontinence (a score of  $>$  or  $=3$  on a validated incontinence severity index -- at least weekly or monthly leakage of more than just drops) and posited that it reflected the population of women more likely to seek treatment. Moderate to severe SUI was reported to affect 6.9% of women 20 to 39 years old, 17.2% in 40 to 59 years old, 23.3% in those 60 to 79 years old, and 31.7% in women 80 years or older. (Nygaard I, et al.

Pelvic Floor Disorders Network. Prevalence of symptomatic pelvic floor disorders in US women. JAMA. 2008; 300:1311-6.) The prevalence was also found to increase with childbirth and for women who were overweight or obese.

In a study of women presenting with noncancerous gynecologic conditions, just over half had symptoms of coexisting urinary incontinence, and on average, an additional 4% developed UI each year. (Wu JM, et al. Prevalence and incidence of urinary incontinence in a diverse population of women with noncancerous gynecologic conditions. Female Pelvic Med Reconstr Surg. 2010; 16:284-289.) Many women reported symptoms of urinary urgency, nocturia and incomplete bladder emptying. Additionally, it was noted that less than half of women with incontinence advise their healthcare providers of their symptoms. This often may be because of the embarrassment and stigma associated with incontinence. (Stress Urinary Incontinence, A Monograph from the AUA Foundation 2011).

Urinary incontinence can adversely affect the well-being of women and cause distress and embarrassment, with lifestyles, relationships and careers being profoundly implicated. SUI can lead women to isolate themselves, to limit their work and social life, and curtail activities such as trips, exercise and attending family and other social gatherings. Studies have shown that SUI imparts adverse psychosocial impacts, social embarrassment and avoidance and limiting behaviors, including depression and anxiety about having sex and engaging in numerous other activities. (Fultz NH, et al. Burden of stress urinary incontinence for community-dwelling women. Am J Obstet Gynecol. 2003;

189:1275-82). Urinary incontinence can lead to urinary tract infections, cellulitis, pressure ulcers, sleep deprivation, social withdrawal, depression, and sexual dysfunction.

The diagnosis of SUI is based on involuntary urine loss from the urethra coincident with increased abdominal pressure (positive stress test) such as that occurring during coughing and straining in a patient who complains of stress incontinence. (Dmochowski RR, et al. Update of AUA guideline on the surgical management of female stress urinary incontinence. J Urol. 2010; 183:1906-14 (2010 AUA SUI Guidelines)). Urodynamics may also be used to diagnose or confirm SUI.

#### B. Non-Surgical Treatment of SUI

SUI may be treated in different ways, including lifestyle changes/behavioral therapy, non-surgical treatment and surgical treatment. Lifestyle and behavioral therapies include bladder training, scheduled toilet trips, fluid and diet management, weight loss, smoking cessation, and modification of medications in the case of side effects. These therapies can be combined with others. There are no FDA-approved medications for the treatment of SUI.

Nonsurgical options include behavior muscle therapy (Kegel exercises) and the use of a pessary, which is a device inserted into the vagina to support the pelvic area and urethra to relieve mild symptoms. Kegel exercises have shown to improve mild to moderate urge and stress incontinence. Approximately 65% will experience some improvement, but only 15-28% of women have a 100% cure rate (no incontinence

episodes) and after 3-15 years, 25-50% will have undergone surgery. (Labrie J, et al. Protocol for Physiotherapy Or TVT Randomised Efficacy Trial (PORTRET): a multicentre randomized controlled trial to assess the cost-effectiveness of the tension free vaginal tape versus pelvic floor muscle training in women with symptomatic moderate to severe stress urinary incontinence. BMC Womens Health. 2009; 9:24, citing Alewijnse D, et al. Effectiveness of pelvic floor muscle exercise therapy supplemented with a health education program to promote longterm adherence among women with urinary incontinence. Neurourol Urodyn 2003; 22:284-295; Goode PS, et al. Effect of behavioral training with or without pelvic floor electrical stimulation on stress incontinence in women: a randomized controlled trial. JAMA 2003; 290:345-352; Cammu H, et al. Who will benefit from pelvic floor muscle training for stress urinary incontinence? Am J Obstet Gynecol 2004; 191:1152-1157; Bo K, et al. Lower urinary tract symptoms and pelvic floor muscle exercise adherence after 15 years. Obstet Gynecol 2005; 105:999-1005; Lamers BH & Vaart CH van der. Medium-term efficacy of pelvic floor muscle training for female urinary incontinence in daily practice. Int Urogynecol J Pelvic Floor Dysfunct 2007; 18:301-307.)

Pessaries must be removed for cleaning or sexual activity and can lead to vaginal discharge, odor, pain, bleeding and erosion. Like pelvic floor exercises, many women discontinue pessary use. In a one year randomized trial, only 45% of women reported that they were still using the pessary at one year and only 57% of women reported that they were continuing to practice their pelvic floor muscle exercises. (Richter HE, A Trial

of Continence Pessary vs. Behavioral Therapy vs. Combined Therapy for Stress Incontinence (ATLAS); Obstet Gynecol. 2010; 115:609–617.)

#### C. Bulking Agents

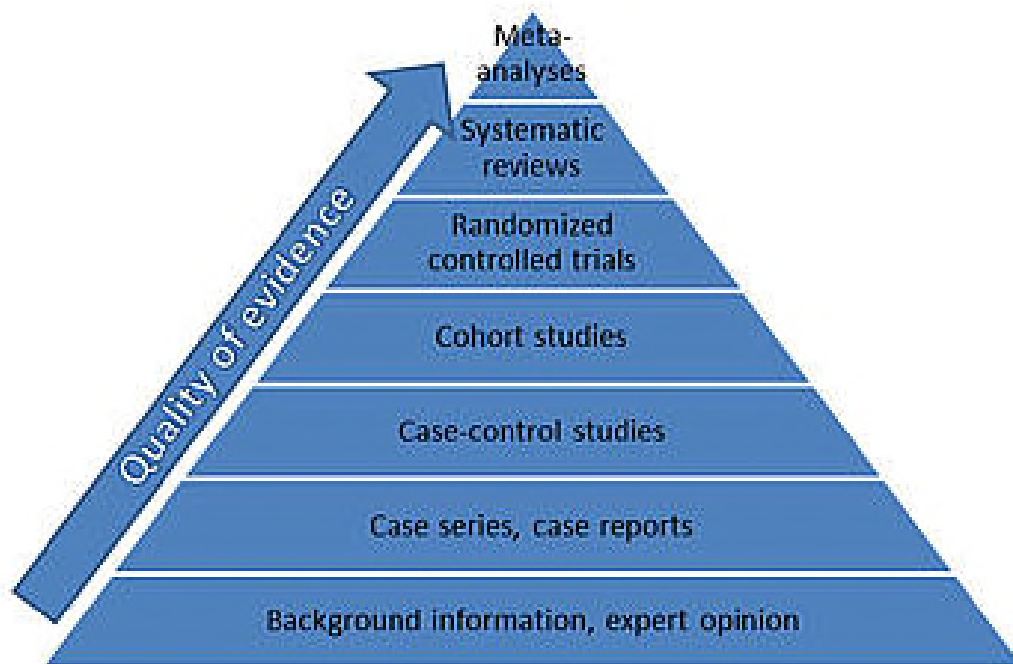
Injectable agents (bulking agents), like collagen, are sometimes used to treat SUI. The agent is injected into tissues around the upper portion of the urethra. This is usually performed under anesthesia, frequently local, via a cystoscope which is passed through the urethra. These agents work by bulking the area around the urethra. Injectable agents are not a permanent repair and efficacy is lower than that achieved with surgery. Fewer than 4 out of 10 women have long-term benefits. The cured/dry estimates for patients treated with collagen decrease from 48% at 12-23 months to 32% at 24-47 months. (AUA SUI Guidelines 2010). Many women will need multiple injections to maintain continence, and the main risks are pain at the injection site, injury to the urethra, and migration of the bulking material.

#### D. Surgical Treatment of SUI -- TVT / TVT-O

Surgery for SUI has been shown to be the most definitive treatment. Surgery for SUI includes the Burch colposuspension, native/biologic tissue slings and most often, synthetic slings. Monofilament, large pore polypropylene like that used in TVT and TVT-O, is the most common type of synthetic material used in slings.

The TVT and TVT-O slings have been studied extensively, in over 100 randomized controlled trials (RCTs) and many more other studies, systematic reviews, Cochrane

Reviews, metaanalyses, professional society guidelines, analyses, reviews, and position statements. These data are of the highest level of medical and scientific evidence pursuant to the Oxford Levels of Evidence as shown below in the levels of evidence pyramid:

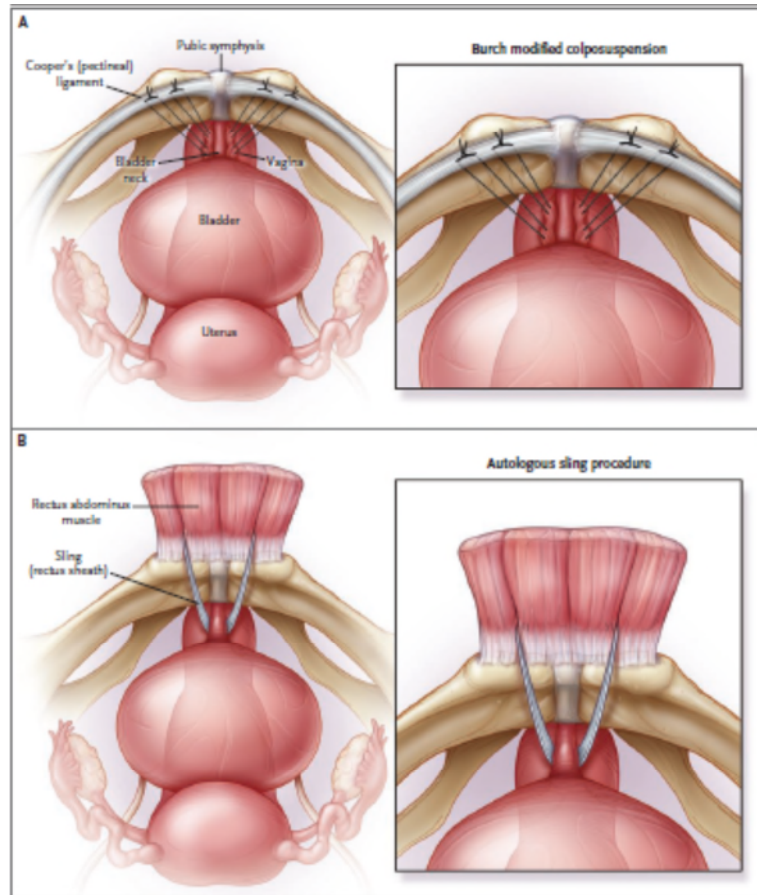


(<http://www.cebi.ox.ac.uk/for-practitioners/what-is-good-evidence.html>)

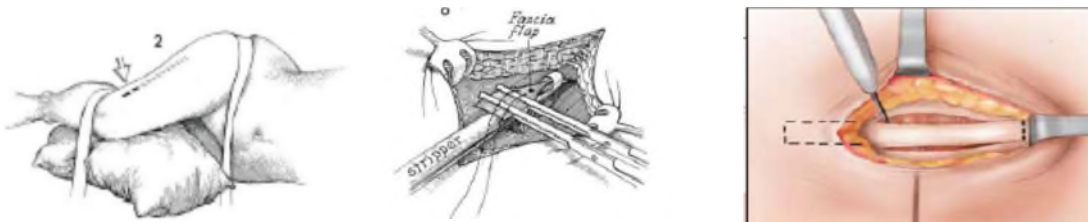
My opinions are based on these high level data and thus my opinions are evidence based, unlike to Plaintiffs' experts who rely on materials which are of the lowest level evidence such as case reports and case series, and in many cases simply irrelevant such as emails, documents, literature and excerpts of testimony concerning hernia mesh and prolapse devices.

The data on the TVT and TVT-O surpasses that of other procedures like the Burch colposuspension and the autologous pubovaginal sling, as well as all other slings. Of all the sling procedures, the Type 1 macroporous, monofilament, polypropylene mesh used in the TVT and TVT-O has the longest and broadest track record of safe and effective use. Other types of surgeries to treat SUI in the past, such as Marshall-Marchetti-Krantz (MMK) procedure, anterior colporrhaphy and needle suspension procedures, have declined and are not now recommended by the pertinent medical associations.

The Burch colposuspension procedure can be performed open or laparoscopically under general anesthesia. Access to the bladder and urethra is achieved by making an incision in the abdominal wall. In the Burch, the vaginal wall is attached to the Cooper's ligament next to the pubic bone. Cystoscopy may also be performed during the Burch. Patients are required to stay in the hospital longer than for a TVT procedure, which can be performed with local or regional anesthetic. Surgery and recovery times are longer with the Burch compared to the TVT. Although the laparoscopic approach to the Burch is available to some physicians, disadvantages include the difficulty in teaching the technique, a steep learning curve for laparoscopic suturing, the requirement for general anesthesia, abdominal entry, pneumoperitoneum, and three or four abdominal incisions.



The pubovaginal sling procedure is usually performed using general anesthesia. This sling requires an abdominal incision to harvest a rectus fascia graft or leg incisions to harvest a fascia lata graft. This can be done with a scalpel, electrocautery or with the aid of a tissue stripper.



Cadaveric slings are not commonly used because of decreased efficacy and lack of durability (resorption and integration risks) and issues with rejection and questions of durability of xenogenic (mostly porcine) tissue slings also limits their use. After a vaginal incision is made, Stamey needles or long clamps are passed from the abdominal incision through the retropubic space. After cystoscopy, the harvested strip of fascia is pulled up transvaginally and the sling is tensioned with a surgical instrument similar to that with a TVT and attached to the rectus fascia with permanent sutures.

While some of plaintiffs' experts claim that another material such as PVDF, Vypro or Ultrapro should be used, they point to no similar breadth and length of clinical data in SUI patients to make such comparisons nor have they provided data showing that these meshes would work long term in the design of the TVT or TVT-O which have long term data. The reason is simple – they cannot. These meshes have not been studied to treat SUI in women like TVT and TVT-O. Their methodology is severely compromised and in effect, unscientific. I know of no pelvic floor surgeons in the state of Texas or in the United States who use PVDF or kits employing PVDF to treat SUI or mixed UI. The same can be said for Vypro and Ultrapro mesh.

Urology, gynecology and urogynecology specialists and surgeons like me turn to the TVT and TVT-O because it is proven and it works. It is endorsed by urology, gynecology and urogynecology professional societies in the United States, Europe and internationally whereas Plaintiffs' experts' posited alternative mesh design for SUI are not. Also while Vypro, Gynemesh PS and Ultrapro mesh have been suggested as

potential better design, I would have concern with a potential decrease of efficacy if utilized as a sling given the mesh in a SUI sling is only about 1 centimeter wide. This narrow strip of tape needs pores like that in the TVT and TVT-O mesh as the mesh provides for a backboard at the midurethra. Vypro and Ultrapro also have a partially absorbable component and the data do not show that these meshes would work in the TVT design as the mesh sticks to the sheath and tears apart upon sheath removal, losing integrity. Moreover, when used in pelvic organ prolapse repair they have not been demonstrated to be more efficacious or safer and have exposure rates of 15% and dyspareunia. (Jacquetin 2004 ICS; Milani 2012)

The pore size for the TVT and TVT-O mesh is macroporous (> 75 microns) and allows the cells needed to address bacteria and promote tissue incorporation. Plaintiffs' experts' claim that 1,000 microns are needed in each direction in order for a mesh to have effective porosity is a theory and artificial construct and the clinical data on the TVT and TVT-O mesh as discussed later is inconsistent with this theory. Moreover, the porosity of the TVT and TVT-O mesh is among the largest for any SUI sling and is optimal for use in the TVT configuration. Lastly, these other meshes can also lead to mesh exposure, which is a wound complication.

There are risks with all surgeries. All SUI surgeries have potential risks. All surgical procedures to treat SUI can fail. All surgical procedures have some degree of pain and discomfort. All surgical procedures to treat SUI may require reoperation for failure or to treat complications. For example, as discussed later in the SISTER trial that

was conducted by the Urinary Incontinence Network, 47% of the Burch patients and 63% of the fascial sling patients had adverse events. (Albo ME, Burch colposuspension versus fascial sling to reduce urinary stress incontinence. N Engl J Med. 2007; 356:2143-55.)

The risks of SUI surgery include:

Damage to organs like the bladder	Erosion of suture (ie, into bladder)
Ureteral injury	Urinary tract infection (recurrent)
Damage to bowel	Recurrent cystitis (urinary bladder inflammation)
Damage to vessels	Catheter complications
Damage to nerves	Voiding dysfunction / difficulty
Anesthesia risks	De novo detrusor overactivity
Wound complications some requiring surgical intervention	De novo urgency urinary incontinence
Infection	Urinary retention
Incisional hernia	Urinary frequency
Wound dehiscence (wound edge separation)	Need for self-catheterization
Seroma or hematoma	Persistent Voiding dysfunction
Granulation tissue or stitch granulations	Voiding dysfunction leading to surgical revision
Inflammation	Pain
Bleeding	Pain to the groin
Need for blood transfusion	Pelvic pain
Blood clot	Dyspareunia (Pain with sex)
DVT	Numbness or weakness from the surgery
Fistula	Gastrointestinal problems

Bowel adhesion	Development of vaginal wall prolapse after Burch surgery
Ileus / bowel obstruction.	
Abdominal scar	Need for repeat surgery

Urologists, Ob/Gyns and urogynecologists are trained on the risks of these surgeries in residency and fellowship. SUI surgery, including the TVT and TVT-O, are taught at many residencies and fellowship programs in the United States and Texas specifically. Mesh exposure/erosion is the only unique complication of the TVT and TVT-O as compared to other SUI surgeries. (FDA March 27, 2013 Statement, Considerations about Surgical Mesh for SUI; AUA October 2013 Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence). Moreover, colposuspension and fascial sling procedures rely on the use of permanent sutures, which can also lead to erosion, and wound complications also occur with these procedures. In particular the large abdominal incision is susceptible to wound herniation, seroma and infection and leads to scarring. Pain and nerve injury can also occur with the incision and secondary surgical site harvesting of fascia lata as well. Voiding dysfunction after SUI surgery, and associated with tensioning of sutures and biologic and synthetic slings, can occur with all SUI surgeries. Pain and dyspareunia can occur with all SUI surgeries, as can organ damage and bladder perforation. Knowledge of these risks is a basic part of female pelvic surgery training and from my standpoint as a medical doctor, these risks do not need to be incorporated into the TVT-O IFU. Surgeons would be aware of these risks from their basic training and experience.

Moreover these risks are obvious to pelvic floor surgeons performing SUI surgeries given the described surgical techniques and instruments and materials used during SUI surgery.

The Burch colposuspension procedure and the pubovaginal sling, using autologous rectus fascia, were studied in the SISTER trial. (Albo ME., N Engl J Med. 2007;356:2143-55.) 520 of 655 women (79%) completed the outcome assessment. At 24 months, cumulative success rates were higher for women who underwent the fascial sling procedure than for those who underwent the Burch procedure, for both the overall category of success (47% vs. 38%,  $P=0.01$ ) and the category specific to stress incontinence, which included no self-reported symptoms of stress incontinence, a negative stress test, and no retreatment for stress incontinence (66% vs. 49%,  $P<0.001$ ).

Moreover, as reported in Figure 4, at 2 years the failure rate was 70% with the Burch and 57% for the sling in the overall category, and the failure rate for SUI specific criteria was 59% with the Burch and 40% with the fascial sling. Overall adverse events were higher with the fascial sling procedure (63% vs 49% in the Burch group) and more women in the fascial sling group had urinary tract infections, difficulty voiding, and postoperative urge incontinence. In the extended SISTER trial, urinary continence rates decreased during a period of 2 to 7 years postoperatively from 42% to 13% in the Burch group and from 52% to 27% in the sling group, respectively. (Richter H, et al. Patient Related Factors Associated with Long-Term Urinary Continence After Burch

Colposuspension and Pubovaginal Fascial Sling Surgeries. J Urol. 2012; 188:485-9.) This study shows that rates with both procedures continue to decline over the longer term.

The TVT device was revolutionary in the field of SUI surgery. It was designed and developed by surgeons over many years of study. (Petros P. Creating a gold standard surgical device: scientific discoveries leading to TVT and beyond: Ulf Ulmsten Memorial Lecture 2014. Int Urogynecol J. 2015; 26:471-6.) Testing led to the development of the Integral Theory and numerous meshes such as Mersilene, Gore-Tex, Teflon and Marlex were tried in the device that would become the TVT, but with higher levels of erosion and tape rejection. (Petros PE, Ulmsten UI. An integral theory and its method for the diagnosis and management of female urinary incontinence. Scand J Urol Nephrol Suppl. 1993; 153:1-93; Ulmsten U, et al. An ambulatory surgical procedure under local anesthesia for treatment of female urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 1996; 7:81-5; Falconer C, et al. Influence of different sling materials on connective tissue metabolism in stress urinary incontinent women. Int Urogynecol J Pelvic Floor Dysfunct. 2001; 12 Suppl 2:S19-23.) Mersilene tape was found to induce a significant inflammatory reaction in paraurethral tissues, with a significant increase in collagen solubility by pepsin. (Falconer C, et al. Clinical outcome and changes in connective tissue metabolism after intravaginal slingplasty in stress incontinent women. Int Urogynecol J Pelvic Floor Dysfunct. 1996; 7:133-7.)

By 1996 the macroporous Prolene polypropylene mesh tape was found to be optimal for use in the TVT as a 1cm wide piece of tape covered by a protective sheath,

with high efficacy, low morbidity and low rates of mesh exposure. A tissue reaction study in women showed that there was proper tissue integration and minimal inflammatory reaction. (Falconer C, et al. Influence of different sling materials on connective tissue metabolism in stress urinary incontinent women. *Int Urogynecol J Pelvic Floor Dysfunct.* 2001; 12 Suppl 2:S19-23.) The authors reported there was practically no tissue reaction at all seen 2 years after TVT surgery when Prolene mesh was used (Fig. 3), no tape rejections, and there was no change in collagen extractability in the Prolene group (Fig. 1). Additionally, there were no histological differences between paraurethral connective tissue in biopsies from patients operated on with Prolene tape and in controls 2 years after surgery. Lastly, there was no statistical difference in collagen concentration or extractability. Conversely, Mersilene showed two rejections, an intense inflammatory response, and a significant increase in collagen extractability by pepsin. By the time that TVT-O was released, the TVT had been successfully utilized in hundreds of thousands of patients, demonstrating high efficacy, a minimally invasive placement and low morbidity and complications. The TVT-O sling uses the same macroporous Prolene polypropylene mesh as the TVT.

Data cited in my report shows the macroporous Prolene polypropylene mesh tape used in the TVT and TVT-O to be universally accepted as the best material and most biocompatible for use in SUI. These include the highest levels of evidence such as Cochrane reviews, SUI Guidelines, systematic reviews and metaanalyses, and RCTs. Cochrane Reviews are systematic reviews of primary research in human health care and health policy, and are internationally recognized as the highest standard in evidence-

based health care. They investigate the effects of interventions for prevention, treatment and rehabilitation. (<http://community.cochrane.org/cochrane-reviews>)

For example the Ford 2015 Cochrane Review included 81 trials that evaluated 12,113 women the majority of which concerned the TVT and TVT-O devices. (Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015 Jul 1;7:CD006375. PMID: 26130017.) They found that MUS have been the most extensively researched surgical treatment for SUI in women and have a good safety profile. Irrespective of the routes traversed, they are highly effective in the short and medium term, and accruing evidence demonstrates their effectiveness in the long term. This review illustrates their positive impact on improving the quality of life of women with SUI. With the exception of groin pain which mostly resolved in the first 6 months, fewer adverse events occur with employment of a transobturator approach. The trials showed that over 80% of women with stress urinary incontinence are cured, or have significant improvement in their symptoms, with either operation, for up to five years after surgery. There is moderate quality evidence that overall reported rates of tape-related complications are low, such as erosion of the tape into the vagina at about 2% for both routes of tape insertion. The reported occurrence of problems with sexual intercourse including pain was low, and leakage of urine during intercourse are improved following insertion of these tapes.

At page 45, they also assessed complication rates derived from several registries involving thousands of patients, again the majority of whom received a TVT or TVT-O device, and reported low rates that were consistent with their primary analysis:

<b><u>Event</u></b>	<b><u>TVT</u></b>	<b><u>TVT-O / TOT</u></b>
Bladder perforation	2.7 - 3.9%	0.4%
Reoperation rates relating to tape insertion or voiding dysfunction	1.6 – 2.4%	0.8 – 2.2%
Urinary retention	1.6%	0.5%
Pelvic hematoma	0.7 – 1.9%	0.5%
Infection rate	0.7%	0.6%
Vaginal tape erosion / extrusion	1.5%	0.4%
Groin pain	0.4%	1.6%

Additionally, Ford reported that type 1 mesh like that in TVT and TVT-O:

has the highest biocompatibility with the least propensity for infection. Differences in their efficacy and complications are likely to be due to several factors including the different knits and weaves of the various tape materials, their biomechanical properties and histological biocompatibility. Pore size affects the inflammatory response and resultant connective tissue formation within and into the mesh, and the rearrangement of materials such as collagen within the mesh structure. Macroporous meshes (pore size in excess of 75  $\mu$ m) easily allow macrophages, leukocytes, fibroblasts, blood vessels and collagen to transverse the pores: thus macroporous meshes promote tissue host ingrowth with resultant biocompatibility and low risk of infection (Amid P. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia 1997; 1:15–21). Monofilament tapes are widely available and now predominate in current clinical practice.

As a result, macroporous, monofilament Prolene polypropylene mesh and the TVT and TVT-O have been specifically recommended for SUI treatment in light of the large body of data supporting the devices. (NICE (National Institute for Health and Care

Excellence) Clinical Guideline 171 - Urinary incontinence: The management of urinary incontinence in women, Sept. 2013). The NICE SUI Guideline recommends that when offering a synthetic mid-urethral tape procedure, surgeons should:

- use procedures and devices for which there is current high quality evidence of efficacy and safety <sup>11</sup>
- only use a device that they have been trained to use
- use a device manufactured from type 1 macro porous polypropylene tape
- consider using a tape coloured for high visibility, for ease of insertion and revision.

Footnote 11 referenced above states that the guideline only recommends the use of tapes with proven efficacy based on robust RCT evidence and identified TVT and TVT-O as meeting these criteria.

As noted above, the TVT and TVT-O include a macroporous (large pore > 75 microns), monofilament polypropylene mesh covered with a sheath that is attached to trocars / helical passers. The TVT is inserted via vaginal incision retropubically and the TVT-O is inserted via vaginal incision through the obturator (it is an “inside-out” transobturator passage). The sling is not anchored. Instead, tissue grows into the mesh and the mesh is held in place.

The sling works by providing support to the urethra, for example, when a woman coughs, sneezes or exercises. During TVT placement cystoscopy is performed to detect potential bladder perforation, a potential risk that is well known, warned of, and easy to manage intraoperatively. With the TVT-O, which passes through the obturator foramen, a cystoscopy is not needed, but surgeons are always free to perform one if they choose to do so. While plaintiffs’ experts seem to take issue with blind passage of instruments,

similar procedures are used during the placement of an autologous sling. Moreover, the Burch colposuspension which is performed in an open manner can lead to bladder and bowel injury. (Schimpf MO, et al. Society of Gynecologic Surgeons Systematic Review Group. Sling surgery for stress urinary incontinence in women: A systematic review and meta-analysis. Am J Obstet Gynecol. 2014; 211:71.e1-71; AUA 2012 update to SUI Guidelines. <https://www.auanet.org/common/pdf/education/clinical-guidance/Incontinence.pdf>) Overall the rates of serious complications is less with TVT and TVT-O.

The sling is placed in the space between the vaginal wall and the urethra. When placed as described in the standard fashion, it does not traverse near the bladder or urethra. The mesh is taught to be placed tension-free at the midurethra with the aid of a blunt instrument between the urethra and sling, the sheath is removed, the ends are cut, the excess mesh is excised, and the small incisions are closed.

While plaintiffs' experts make claims about particle loss, I have not observed this clinically and even if particles were to get into the vagina, there would be no clinically significant effect. The particles are of the same Prolene polypropylene that make up the mesh. Moreover, Prolene polypropylene has long been used as a suture in various applications for decades. The clinical data on TVT and TVT-O also do not describe particle loss as playing any significant role on efficacy, which is high, or complications, which are low as discussed in my report. Also, during the surgery the site can be irrigated and suctioned, which would dispose of any particles. Their claims regarding

significant stretching of the mesh as seen on a machine in a lab leading to particle loss, mesh roping and curling are also not clinically significant. The mesh is not used in this manner clinically, as the bench testing removes the trocar, which provides a pathway for the mesh to traverse, and also removes the protective sheath. The protective sheath over the mesh bears the forces as the mesh is passed through the pelvis and as noted the mesh is placed tension free and spaced from the urethra with an instrument like a dilator before removing the sheaths. Also, surgeons do not pre-stretch the mesh to 50% elongation before placement of the TVT and TVT-O. Additionally, the mesh can be repositioned or replaced during the procedure. Mesh particles seen in packaging are also of no clinical concern for these reasons.

The macroporous Prolene polypropylene mesh cut to 1.1cm in width is a lightweight mesh in the TVT and TVT-O design application for the treatment of SUI. As noted in the January 2014 AUGS & SUFU (Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction) Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence, "As a knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years [8]." Notably, reference 8 refers to the 17 year study of the TVT mesh. (Nilsson CG, et al. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. 2013; 24:1265-69).

The Nilsson 17 year study of the TVT mesh demonstrated excellent efficacy over the long term and very low complications. Objective cure, defined as a negative stress test, was seen in 42 out of 46 women (91.3 %). Two of the women with a positive stress test were regarded as failures, while one woman considered herself significantly improved, even though she had minimal leakage at her stress test. 87.2 % regarded themselves cured or significantly better than before surgery and 50 out of 51 (98 %) would recommend the TVT procedure to a friend. The single tape complication seen during this prospective observational trial during a 17-year period was a small symptom-free exposure of the tape in a completely asymptomatic, continent and highly satisfied 69-year-old woman with an atrophic vaginal mucosa. She was prescribed local estrogen therapy. No other adverse effects, signs or reactions of the tape material could be detected among the women examined. These data have been replicated in several other studies assessing the TVT and TVT-O as discussed in my report.

The Nilsson 17 year study also showed that there was no shrinkage of the TVT mesh over time, as suggested by PVR volumes within normal ranges, except for 2 patients with concomitant diseases (Parkinson's, grade III cystocele). Similar data are seen in another prospective study where unchanged resting Q-tip angles confirm the tension-free concept of TVT and there was no shrinkage or tightening of the sling. (Lukacz ES, et al. The effects of the tension-free vaginal tape on proximal urethral position: a prospective, longitudinal evaluation. *Int Urogynecol J Pelvic Floor Dysfunct.* 2003; 14:179-84.) Other sling materials, such as cadaveric fascia, have been associated with significant tissue reaction and have been shown to shrink over time (Fokaefs ED, et

al. Experimental evaluation of free versus pedicled fascial flaps for sling surgery of urinary stress incontinence. J Urol 1997; 157:1039–1043). The authors noted that the TVT seems to be more elastic and associated with less tissue reaction than other materials. Falconer evaluated the TVT material in postoperative biopsy specimens from women undergoing the procedure and found minimal inflammation without a significant change in collagen solubility or significant foreign-body reaction. (Falconer C, et al. Influence of different sling materials on connective tissue metabolism in stress urinary incontinent women. Int Urogynecol J Pelvic Floor Dysfunct. 2001; 12 Suppl 2:S19-23.) Moreover, the low complication rates seen long term also contradict Plaintiff's experts' claims that the TVT mesh significantly contracts.

The TVT-O has been in use for almost 10 years now and the TVT sling has been in use for over 15 years now. It is my opinion that the TVT and TVT-O are the gold standard and current standard of care for the treatment of SUI. It is my opinion that the TVT and TVT-O are safe and effective. My opinions are supported by the major urologic and urogynecologic surgeon associations and societies. (NICE (National Institute for Health and Care Excellence) Clinical Guideline 171 - Urinary incontinence: The management of urinary incontinence in women, Sept. 2013; AUA Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence, Oct. 2013; AUGS Position Statement on Restriction of Surgical Options for Pelvic Floor Disorders, March 2013; AUGS & SUFU (Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction) Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence, Jan. 3, 2014; IUGA (International Urogynecological

Association) Position Statement on Mid-Urethral Slings for Stress Urinary Incontinence, July 2014; Schimpf MO, et al. Society of Gynecologic Surgeons Systematic Review Group. Sling surgery for stress urinary incontinence in women: A systematic review and meta-analysis. Am J Obstet Gynecol. 2014; 211:71.e1-71.).

The AUA October 2013 Statement, which I agree with, concluded that:

Suburethral synthetic polypropylene mesh sling placement is the most common surgery currently performed for SUI. Extensive data exist to support the use of synthetic polypropylene mesh suburethral slings for the treatment of female SUI, with minimal morbidity compared with alternative surgeries. Advantages include shorter operative time/anesthetic need, reduced surgical pain, reduced hospitalization, and reduced voiding dysfunction. Mesh-related complications can occur following polypropylene sling placement, but the rate of these complications is acceptably low. Furthermore, it is important to recognize that many sling-related complications are not unique to mesh surgeries and are known to occur with non-mesh sling procedures as well. It is the AUA's opinion that any restriction of the use of synthetic polypropylene mesh suburethral slings would be a disservice to women who choose surgical correction of SUI. Additionally, both the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) and the AUA support the use of multi-incision monofilament midurethral slings for the treatment of SUI in properly selected patients who are appropriately counseled regarding this this surgical procedure by surgeons who are trained in the placement of such devices, as well as the recognition and management of potential complications associated with their use.

Multiple case series and randomized controlled trials attest to the efficacy of synthetic polypropylene mesh slings at 5-10 years. This efficacy is equivalent or superior to other surgical techniques. There is no significant increase in adverse events observed over this period of followup. Based on these data, the AUA Guideline for the Surgical Management of Stress Urinary Incontinence (2009) concluded that synthetic slings are an appropriate treatment choice for women with stress incontinence, with similar efficacy but less morbidity than conventional nonmesh sling techniques.

The March 2013 AUGS Position Statement similarly concluded based on high level evidence that full-length midurethral slings, both retropubic and transobturator,

have been extensively studied, are safe and effective relative to other treatment options and remain the leading treatment option and current gold standard of care for stress incontinence surgery.

In 2014, SUFU which has over 500 members, and AUGS which has over 1,700 members, issued a Position Statement which analyzes high level data including level 1 Cochrane Review, RCTs and long term study of the TVT mesh and discusses the acceptance and utility of the TVT and TVT-O midurethral slings. They observe that “The polypropylene mesh midurethral sling is the recognized worldwide standard of care for the surgical treatment of stress urinary incontinence. The procedure is safe, effective, and has improved the quality of life for millions of women.” I am in agreement with this statement.

My review of the literature and clinical experience are consistent with their conclusion and the basis for the conclusion, and with which I agree:

#### Justification for the Position Statement

##### 1. Polypropylene material is safe and effective as a surgical implant.

Polypropylene material has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of patients in the US and the world (personal communication with manufacturers of polypropylene suture and mesh). As an isolated thread, polypropylene is a widely used and durable

suture material employed in a broad range of sizes and applications. As a knitted material, polypropylene mesh is the consensus graft material for augmenting hernia repairs in a number of areas in the human body and has significantly and favorably impacted the field of hernia surgery. [6, 7] As a knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years [8].

2. The monofilament polypropylene mesh MUS is the most extensively studied anti-incontinence procedure in history.

A broad evidence base including high quality scientific papers in medical journals in the US and the world supports the use of the MUS as a treatment for SUI [9]. There are greater than 2000 publications in the scientific literature describing the MUS in the treatment of SUI. These studies include the highest level of scientific evidence in the peer reviewed scientific literature [9]. The MUS has been studied in virtually all types of patients, with and without comorbidities, and all types of SUI. Multiple randomized, controlled trials comparing types of MUS procedures, as well as comparing the MUS to other established non-mesh SUI procedures, have consistently demonstrated its clinical effectiveness [9-12] and patient satisfaction [12]. Among historical SUI procedures, the MUS has been studied as long in follow-up after implantation as any other procedure and has demonstrated superior safety and efficacy [8]. No other surgical treatment for SUI before or since has been subject to such extensive investigation.

3. Polypropylene mesh midurethral slings are the standard of care for the surgical treatment of SUI and represent a great advance in the treatment of this condition for our patients.

Since the publication of numerous level one randomized comparative trials, the MUS has become the most common surgical procedure for the treatment of SUI in the US and the developed world. This procedure has essentially replaced open and transvaginal suspension surgeries for uncomplicated SUI. There have been over 100 surgical procedures developed for the management of SUI and there is now adequate evidence that the MUS is associated with less pain, shorter hospitalization, faster return to usual activities, and reduced costs as compared to historic options that have been used to treat SUI over the past century. Full-length midurethral slings, both retropubic and transobturator, have been extensively studied, are safe and effective relative to other treatment options and remain the leading treatment option and current gold standard for stress incontinence surgery [13]. Over 3 million MUS have been placed worldwide and a recent survey indicates that these procedures are used by > 99% of AUGS members [14].

4. The FDA has clearly stated that the polypropylene MUS is safe and effective in the treatment of SUI.

The midurethral sling was not the subject of the 2011 FDA Safety Communication, "Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Vaginal Placement for Pelvic Organ Prolapse." [3]. In this document, it was explicitly

stated: “The FDA continues to evaluate the effects of using surgical mesh for the treatment of SUI and will report about that usage at a later date.” In 2013, the FDA website stated clearly that: “The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year.” [5].

Conclusion: The polypropylene midurethral sling has helped millions of women with SUI regain control of their lives by undergoing a simple outpatient procedure that allows them to return to daily life very quickly. With its acknowledged safety and efficacy it has created an environment for a much larger number of women to have access to treatment. In the past, concerns over failure and invasiveness of surgery caused a substantial percent of incontinent women to live without treatment. One of the unintended consequences of this polypropylene mesh controversy has been to keep women from receiving any treatment for SUI. This procedure is probably the most important advancement in the treatment of stress urinary incontinence in the last 50 years and has the full support of our organizations which are dedicated to improving the lives of women with urinary incontinence.

IUGA, which represents surgeons practicing around the world, has also analyzed the high level data on polypropylene midurethral slings and in particular TVT and TVT-O. It is important to note that the vast majority of high level data are on the TVT and TVT-O device, as they have the most randomized controlled trials and longest follow up and the studies, RCTs, Cochrane reviews and metaanalyses cited by IUGA in their analysis involve TVT and TVT-O. IUGA found that:

Mid-urethral slings are minimally invasive procedures developed in Europe in the 1990s to treat female stress urinary incontinence. These slings are narrow, synthetic polypropylene tapes that are surgically placed beneath the middle part of the urethra (water pipe) to provide dynamic support to stop leakage from the bladder. They have been shown to be as effective as more invasive traditional surgery with major advantages of shorter operating and admission times, and a quicker return to normal activities together with lower rates of complications.<sup>3</sup> This has resulted in MUS becoming the operation of choice in Europe, Asia, South America, South Africa, Australasia<sup>4</sup> and North America<sup>5</sup> for treatment of SUI with several million procedures performed worldwide.

(Cody J, et al. Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence. Health Technol Assess 2003; 7:iii, 1–189.; Lee J, Dwyer PL. Age related trends in female Stress Urinary Incontinence Surgery in Australia – Medicare data 94 – 09. Aust N Z J Obstet Gynaecol 2010; 50:543-49 PMID:21133865; <http://www.augs.org/d/do/2535>.)

IUGA’s analysis of numerous Level 1 Cochrane reviews and a meta-analysis determined that “There is robust evidence<sup>9-11</sup> to support the use of MUS from over 2,000 publications making this treatment the most extensively reviewed and evaluated procedure for female stress urinary incontinence now in use. These scientific publications studied all types of patients, including those with co-morbidities such as prolapse, obesity and other types of bladder dysfunction.” (Ogah J, Cody JD, & Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database Syst. Rev. CD006375 (2009); Rehman H, Bezerra CC, Bruschini H, Cody JD. Traditional suburethral sling operations for urinary incontinence in women. Cochrane Database Syst. Rev. CD001754 (2011); Novara, G., et al., Updated systematic review and meta-analysis of the comparative data on

colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary incontinence. Eur Urol, 2010. 58(2): p. 218-38.)

The TVT and TVT-O slings are taught to residents, fellows and surgeons and in a recent study involving 53 expert urologists and urogynecologists (of whom >90% were fellowship trained) and who could select among many surgical options, the full-length synthetic midurethral sling was the preferred option in 93% for the surgical treatment of primary stress incontinence. (Nager, C.W., et al., A randomized trial of urodynamic testing before stress-incontinence surgery. N Engl J Med 2012; 366:1987-97.) These data are consistent with a recent study carried out in December 2011 that assessed AUGS members' usage of mesh slings, which showed that more than 99% used them before the July 13, 2011 FDA safety update and 96% used them after. (Clemons JL, et al., Impact of the 2011 FDA transvaginal mesh safety update on AUGS members' use of synthetic mesh and biologic grafts in pelvic reconstructive surgery. Female Pelvic Med Reconstr Surg 2013; 19:191-98.) The TVT and TVT-O are safe and effective, easy to teach and learn, and are backed by reams of data, making it the first-line treatment for SUI.

This is also consistent with a study that analyzed case data logs for female incontinence surgeries in 4,185 certifying and recertifying urologists from the American Board of Urology and showed that midurethral slings have been widely adopted by urologists over the last decade. Study data revealed that while traditional procedures decreased from 17% of female incontinence procedures in 2003 to 5% in 2004 to <1%

since 2010 ( $P < .0005$ ), urologists were using more midurethral slings over the same period -- from 3210 procedures in 2003 to 7200 in 2012 ( $P < .0005$ ). (Chughtai BI, et al. Midurethral sling is the dominant procedure for female stress urinary incontinence: analysis of case logs from certifying American Urologists. *Urology*. 2013; 82:1267-71.)

This echoed by the International Continence Society, which includes members from across the world, in their 2013 Stress Urinary Incontinence Fact Sheet, which states “Definitive therapy for SUI is surgical and involves restoring urethral support through use of a sling. Worldwide, midurethral slings comprised of synthetic mesh have become the treatment of choice for SUI. Long-term data are robust and demonstrate durable efficacy with a very low complication rate, particularly in experienced hands.”

As noted earlier, the NICE Clinical Guideline specifically recommends the TVT and TVT-O as suitable first line surgical options because of their robust and high quality evidence. The European Association of Urology also endorses the midurethral sling as the first line treatment option, with which I agree because of its well established safety and effectiveness. (Lucas MG, EAU Guidelines on Surgical Treatment of Urinary Incontinence. *Eur Urol*. 2012; 62:1118-29). The TVT and TVT-O are minimally invasive and less invasive than other surgical options, such as the Burch and native tissue sling.

The Ogah 2009 and 2011 Cochrane Reviews assessed 62 trials involving 7,101 women. Minimally invasive synthetic slings like TVT and TVT-O appeared to be as effective as traditional suburethral slings, but with shorter operating time, and less post-operative voiding dysfunction and de novo urgency symptoms. Midurethral sling

operations were as effective as open retropubic colposuspension with fewer perioperative complications, less postoperative voiding dysfunction, and shorter operative time and hospital stay, but the TVT had significantly more bladder perforations. (Ogah J, et al. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006375; Ogah J, et al. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women: a short version Cochrane review. Neurourol Urodyn. 2011; 30:284-91).

In the Ogah Cochrane Review, monofilament tapes like TVT and TVT-O had higher cure rates compared to multifilament tapes, and fewer tape erosions (1.3% versus 6%). TVT was more effective than top-to-bottom route and incurred significantly less voiding dysfunction, bladder perforations, and tape erosions. No statistically significant difference was found between retropubic and transobturator slings, with patients in both groups reporting an 83% success rate. Objective cure rates at 12 months for 2,434 patients slightly favored TVT (88% versus 84%.) Although statistically significant, this difference is not clinically significant. The Review concluded that current evidence suggested that minimally invasive synthetic suburethral sling operations like TVT and TVT-O are as effective as traditional suburethral slings, open retropubic colposuspension and laparoscopic colposuspension in the short term but with fewer postoperative complications. These data are consistent with the European Association of Urology's recent recommendation of the midurethral sling as a first line surgical option for SUI; it is effective, less invasive, and patients recover more quickly. (Lucas

MG, EAU Guidelines on Surgical Treatment of Urinary Incontinence. Eur Urol. 2012;62:1118-29.)

In November 2015, ACOG and AUGS issued Practice Bulletin 155 – Clinical Management Guidelines concerning Urinary Incontinence in Women. (Urinary incontinence in women. Practice Bulletin No. 155. American College of Obstetricians and Gynecologists. Obstet Gynecol 2015; 126:e66–81.) The purpose of the document was to review information on the current understanding of urinary incontinence in women and to outline guidelines for diagnosis and management that are consistent with the best available scientific evidence. ACOG and AUGS analyzed data and made the following conclusions and practice recommendations to gynecologists and pelvic surgeons, which based on Level A good and consistent scientific evidence, establish that TVT and TVT-O are effective, safe, less invasive than alternatives, and a first line SUI surgery:

- Synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparoscopic colposuspension. Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings. Voiding dysfunction is more common with open colposuspension than with synthetic midurethral slings.
- There are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women.
- Burch colposuspension at the time of abdominal sacrocolpopexy and retropubic midurethral sling at the time of vaginal surgery for pelvic organ prolapse repair

decrease the risk of postoperative stress urinary incontinence in women without preoperative stress urinary incontinence.

Tan conducted a recent meta-analysis of 40 RCTs (minimum duration 12 months) that compared TVT, TVT-O and TOT. (Tan PF, et al. Effectiveness and complication rates of tension-free vaginal tape, transobturator tape, and tension-free vaginal tape-obturator in the treatment of female stress urinary incontinence in a medium- to long-term follow up. Meta-analysis of randomized controlled trials. Saudi Med J. 2014; 35:20-32.) TVT and TVT-O were found to have similar objective and subjective cure rates. The TVT had a higher risk of bladder perforation than TVT-O, and a lower risk of groin/thigh pain than TOT. TVT-O had a lower risk of vaginal erosion than TOT and TOT also had a significantly higher reoperation rate than TVT-O.

The TVT-O and TVT have been studied extensively over the past 15 years and there are numerous 5 and 10+ year studies such as these below that demonstrate their safety and efficacy:

<b><u>Study &amp; Duration</u></b>	<b><u># Pts.</u></b>	<b><u>Objective Success</u></b>	<b><u>Subjective Success</u></b>	<b><u>Other</u></b>
Nilsson 2008 (11 years follow up)	69	90%	77% felt cured and 20% were improved.	93% no leakage on straining. 97% would recommend TVT to a friend.
Liapis 2008 (7 years follow up)	61	80% and 6.5% improved.	78.7% felt cured and 8.1% improved.	
Olsson 2010 (11.5 yrs follow up)	124	84%	77% felt cured and 18% improved.	94% were satisfied (74% very satisfied and 20% satisfied).

<b><u>Study &amp; Duration</u></b>	<b><u># Pts.</u></b>	<b><u>Objective Success</u></b>	<b><u>Subjective Success</u></b>	<b><u>Other</u></b>
Groutz 2011 (10 years follow up)	52	N/A	65% felt cured and 12% improved.	
Aigmueller 2011 (10 years follow up)	141	84% and 8.5% were slightly positive.	57% felt cured and 23% improved.	
Heinonen 2012 (10.5 yrs follow up)	138	90%	78%	
Serati 2012 (10 years follow up)	58	93.10%	89.7% satisfied and 93.1% were improved.	91.4% urodynamic cure rate
Nilsson 2013 (17 years follow up)	58	91.30%	87.2% felt cured or significantly better.	98% would recommend TVT to a friend.
Svenningsen 2013 (10.75 yrs follow up)	483	89.90%	76.1% felt cured and 18% were better. (94.1% improved).	82.6% stated they were very satisfied.
Liapis 2010 (TVT-O 4 years follow up)	115	82% and 7% were improved.	81% cure and 9.4% improvement.	Cough stress test objective cure: TVT-O 85.1% and TVT-O + Ant. Colp. 82.9%.
Angioli 2010 (TVT-O 5 years follow up)	31	73% (89.2% negative cough stress test)	62% reported satisfied or very satisfied.	78.4% would undergo again. Significant improvement in patient satisfaction per VAS scores.
Groutz 2011 (TVT-O 5 years follow up)	61	N/A	N/A	74% cured based on a composite negative CST, no SUI episodes, and positive global satisfaction. An additional 8% were improved.

<b><u>Study &amp; Duration</u></b>	<b><u># Pts.</u></b>	<b><u>Objective Success</u></b>	<b><u>Subjective Success</u></b>	<b><u>Other</u></b>
Cheng 2012 (TVT-O 5.4 years follow up)	100	92%	90.00%	Significant improvement in QOL at 1- and 5-year follow up.
Serati 2013 (TVT-O 5 years follow up)	185	90.80%	90.30%	
Laurikainen 2014 (TVT-O 5 years follow up, RCT)	123	86.20%	85.6% and an additional 6.1% expectations partly met	88.6% would recommend to a friend. Significant improvement in all QOL scores.
Athanasίου 2014 (TVT-O 7.5 years follow up)	124	81.50%	83.5% and an additional 3.2% were improved.	Significant QOL improvement. Objective and subjective cure rates in TVT-O only group 90.3% (28/31).

Recently, Tommaselli published a systematic review and metaanalyses of medium and long term studies, 49 in total, concerning midurethral slings. (Tommaselli GA, et al. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J. 2015; 26:1253-68.) Notably TVT and TVT-O represented the vast amount of data as they were represented in 43 of the 49 studies (Tables 1 and 2). With regard to patient numbers, Table 3 reports that there were 3,974 retropubic (TVT = 3,801) and 2,432 transobturator (TVT-O = 1,375) patients. High objective and subjective cure rates in the long- and medium-term were seen. TVT-O was associated with a significantly lower incidence of vaginal injuries than TOT. There was no difference in persistent pain,

defined as all pain reported beyond the perioperative period (>7 days after procedure), between RP-MUS and TO-MUS (2.2 % vs. 1.9 %). Persistent or chronic pain (i.e. pain persisting beyond the perioperative period or reported at the last follow-up visit) was very rare and reported by 13 patients for RP-MUS (13/3,974 = 0.3%) and 30 patients for TOMUS (30/2,432 = 1.2%). The authors concluded that RPMUS and TO-MUS have similar objective cure rates in the long-term and medium-term but TOTs have a lower subjective cure rate than TVT. This efficacy is backed by a high safety profile, and by a limited number of complications which were seldom severe.

In comparison, in a study including 190 women who underwent open Burch colposuspension, significant urinary incontinence was observed in 56% of patients and only 19% of women remained completely dry at 14 years follow up. (Kjohede, P, et al. Long-term efficacy of Burch colposuspension: a 14-year follow-up study. *Acta Obstet. Gynecol. Scand.* 2008;84:767–72). Another study of the Burch reported a cure rate of 69%, 15% de novo detrusor instability and 24 patients (22 %) still complained of voiding difficulty 10 years or more after the colposuspension with four undergoing urethrotomy. (Alcalay M, et al. Burch colposuspension: a 10-20 year follow up. *Br J Obstet Gynaecol.* 1995; 102:740-5). Though, this study was limited by over 60% loss to follow up.

In a study assessing the Burch in 65 women prospectively at 1.5 years and 155 women retrospectively 4.5 years follow up, cure declined from 87.7% to 77.4%. (Demirci F, et al. Long-term results of Burch colposuspension. *Gynecol Obstet Invest.* 2001; 51:243-7.) The symptom-free cure rate declined 83.9% for 3, 76.2% for 4, 75% for 5 and

68% for 6 years. Demirci reported several other studies that also tended to show that cure with the Burch declined over time comparable to their results:

- Van Geelen et al. [5] reported an objective cure rate after 3 months of 100% and at 1-2 years it was 85%. However, 5 years after the procedure only 75.8% of the women were symptom-free. (van Geelen JM, et al. The clinical and urodynamic effects of anterior vaginal repair and Burch colposuspension. Am J Obstet Gynecol 1988; 159:137-144.)
- Thunedborg et al. [6] reported a complete cure rate of 78.6% for 6 years. (Thunedborg P, et al. Stress urinary incontinence and posterior bladder suspension defects. Results of vaginal repair versus Burch colposuspension. Acta Obstet Gynecol Scand 1990; 69:55-59.)
- Kinn [9] reported 78% for 5 years. (Kinn AC: Burch colposuspension for stress urinary incontinence. Scand J Urol Nephrol 1995; 29:449-455.)
- Eriksen et al. [8] reported 67% for 5 years. (Eriksen BC, et al. Long-term effectiveness of the Burch colposuspension in female urinary stress incontinence. Acta Obstet Gynecol Scand 1990; 69:45-50.)
- Le Bret et al. [10] reported 64% for 5 years. (Le Bret T, et al. Isolated Burch type indirect colposuspension of the bladder neck in the treatment of stress urinary incontinence in women. Long-term results. Prog Urol 1997; 7:426-432.)
- Kjolhede and Ryden [ 11] reported 63% for 6 years. (Kjolhede P, Ryden G. Prognostic factors and long-term results of the Burch colposuspension. Acta Obstet Gynecol Scand 1994; 73:642-647.)
- Christensen et al. [12] reported 33%. (Christensen H, et al. Long-term result of the Stamey bladder neck suspension procedure and of the Burch colposuspension. Scand J Urol Nephrol 1997; 31:349-353.)

As noted above, late complications can occur with the Burch and Demirci reported that at follow up, late complications in the 220 women included dyspareunia in 6, groin or suprapubic pain in 15, cystocele in 18, rectocele in 32 and enterocele in 35.

In a long term RCT of TVT versus the laparoscopic Burch procedure, incontinence rates were similar (57% had subjective urinary incontinence after laparoscopic Burch colposuspension versus 48% after TVT) and 11% of the laparoscopic Burch group and 8% of the TVT group had bothersome SUI. (Jelovsek JE, et al. Randomised trial of laparoscopic Burch colposuspension versus tension-free vaginal tape: long-term follow-up. BJOG. 2008; 115:219–225.)

In a recent multi-center study, initial midurethral-sling surgery including TVT and TVT-O resulted in higher rates of subjective improvement and subjective and objective cure at 1 year when compared with initial physiotherapy involving pelvic-floor muscle training. (Labrie J, et al. Surgery versus physiotherapy for stress urinary incontinence. N Engl J Med. 2013; 369:1124-33.) The study noted that midurethral-sling surgery is a minimally invasive surgical technique for the treatment of stress urinary incontinence with subjective cure rates between 75% and 94% and objective cure rates between 57% and 92%. The procedure is regarded as effective, with minimal complications. A recent well done review of the literature reports numerous high level data which shows the TVT and TVT-O have been significantly studied, are safe and effective, and have acceptable complication rates in my opinion. (Cox A, et al. Surgical management of female SUI: is there a gold standard? Nat Rev Urol. 2013; 10:78-89.)

A large meta-analysis of numerous RCTs comparing the TVT to other SUI surgeries found that the TVT outperformed the Burch colposuspension in terms of postoperative continence rates and success rates were similar after TVT and

pubovaginal slings. (Novara G, et al. Tension-free midurethral slings in the treatment of female stress urinary incontinence: a systematic review and meta-analysis of randomized controlled trials of effectiveness. Eur Urol 2007; 52:663-678.) Similar objective and subjective cure rates were shown between TVT and TVT-O.

The following year, the group performed another meta-analysis which showed lower rates of reoperation for TVT compared to Burch, TVT had more bladder perforations than Burch, and there were similar complications to pubovaginal slings. (Novara G, et al. Complication rates of tension-free midurethral slings in the treatment of female stress urinary incontinence: a systematic review and meta-analysis of randomized controlled trials comparing tension-free midurethral tapes to other surgical procedures and different devices. Eur Urol. 2008; 53:288-308.) In Table 6 of the study, an analysis of over 30 TVT studies, each with a follow up of more than 2 years, showed acceptable rates for complications (the cumulative rates were 1.7% for pelvic hematoma, 3.4% for bladder perforations, 1.1% for vaginal erosion, 0.8% for bladder erosion, 9.7% for urinary tract infections, 15.6% for storage LUTS, 16.1% for voiding LUTS, 4% for clean intermittent catheterization, and 3.2% for reoperations).

More recently, they conducted a meta-analysis of 39 RCTs, which showed that patients receiving midurethral tapes including TVT-R, which was the most studied midurethral sling, and TVT-O, had significantly higher overall and objective cure rates than those receiving Burch colposuspension, although they had a higher risk of bladder perforations. Patients undergoing midurethral tapes and pubovaginal slings had similar

cure rates, although the pubovaginal sling patients were slightly more likely to experience storage lower urinary tract symptoms and had a higher reoperation rate. Retropubic tapes had a slightly higher objective cure rates than the transobturator tapes and subjective cure rates were similar. (Novara G, et al. Updated systematic review and meta-analysis of the comparative data on colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary incontinence. *Eur Urol.* 2010; 58:218–38.)

A meta-analysis comparing TVT-O to TOT found an equal rate of both subjective and objective success rates. Bladder injury and voiding difficulties were less frequent with the TVT-O than the TOT. (Latthe PM, et al. Two routes of transobturator tape procedures in stress urinary incontinence: a meta-analysis with direct and indirect comparison of randomized trials. *BJU Int* 2010; 106:68–76).

The TVT and TVT-O are also effective in cases of mixed incontinence. A systematic review and meta-analysis of six randomized controlled trials and seven prospective non-randomized studies including women with symptomatic and/or urodynamic mixed urinary incontinence showed persistent and good cure of stress component following midurethral sling surgery and cure of the urge component was variable but less than the stress component. (Jain P, et al. Effectiveness of midurethral slings in mixed urinary incontinence: a systematic review and meta-analysis. *Int Urogynecol J.* 2011; 22:923–932.) The cure rate of SUI following MUS was between 85%

and 97%. The overall cure of urgency and UUI component was 30-85% at a follow-up of few months up to 5 years.

The TVT and TVT-O have also shown to be effective in patients with SUI and overactive bladder (OAB). In a prospective multicenter study comparing TVT and TVT-O in treating OAB symptoms using validated objective and subjective measures in women with both SUI and OAB, both TVT and TVT-O resulted in significant improvement in OAB symptoms. (Han JY, Effectiveness of retropubic tension-free vaginal tape and transobturator inside-out tape procedures in women with overactive bladder and stress urinary incontinence. *Int Neurourol J.* 2013; 17:145-51.) The mean number of urgency episodes per 24 hours decreased in both groups. The overall objective cure rates for SUI were 95.2% with TVT and 92.2% in the TVT-O group. Subjective cure rates for SUI were 85% with TVT and 79.6% in the TVT-O group. All subscales of BFLUTSSF (voiding, filling, incontinence, sexual function, and quality of life (QoL)) were improved in both groups, but the improvement in QoL was significantly higher in the TVT group ( $P=0.002$ ). In both groups, urination frequency and nocturia as well as urgency and urgency urinary incontinence (UUI) symptoms were significantly improved after surgery. The cure rates for urgency (53% for TVT vs. 51% for TVT-O) and UUI (55% for TVT vs. 52% for TVT-O) did not differ significantly between the two groups. After surgery, the urgency perception scale (UPS) was also significantly improved. The rates of patient satisfaction were similar at 95.2% in the TVT group and 96.7% in the TVT-O group.

In Laurikainen's five year RCT of TVT (n=131) versus TVT-O (n=123), new-onset urgency incontinence was seen in <3% of the women compared to 80% of the women with preoperative urgency symptoms were relieved of these symptoms 5 years later. (Laurikainen E, et al. Five-year results of a randomized trial comparing retropubic and transobturator midurethral slings for stress incontinence. *Eur Urol*. 2014; 65:1109-14.) These findings suggest that the risk of developing urgency symptoms with or without leakage after TVT and TVT-O is very low and that actually, as discussed earlier, TVT and TVT-O surgery can cure urgency symptoms and is effective in mixed incontinence. (Palva K, Nilsson CG. Prevalence of urinary urgency symptoms decreases by mid-urethral sling procedures for treatment of stress incontinence. *Int Urogynecol J* 2011; 22:1241–7; Abdel-Fattah M, et al. Evaluation of transobturator tension-free vaginal tapes in surgical management of mixed urinary incontinence: 3-year outcomes of a randomized controlled trial. *J Urol* 2014; 191:114–9.). Similarly, another study in women with urodynamically proven stress incontinence and detrusor overactivity who had failed conservative treatment showed a significant reduction in SUI and OAB symptoms (urge urinary incontinence (p<0.001), urgency (p=0.021) and frequency (p=0.014)) after treatment with TVT and TVT-O. (Athanasίου S, et al. Midurethral slings for women with urodynamic mixed incontinence: what to expect? *Int Urogynecol J*. 2013; 24:393-9.)

Sexual activity and function are not negatively impacted by TVT or TVT-O. This is consistent with the recent systematic review and meta-analysis by the Society of Gynecologic Surgeons Systematic Review Group which stated that dyspareunia was rare with the retropubic (<0.001%) and obturator (0.16%) slings. (Schimpf MO, et al. Society

of Gynecologic Surgeons Systematic Review Group. Sling surgery for stress urinary incontinence in women: A systematic review and meta-analysis. Am J Obstet Gynecol. 2014; 211:71.e1-71.) Overall the rates were lower than for the pubovaginal sling:

**TABLE 3**  
**Rates of AEs by sling type analyzed from randomized controlled trials and included AE studies<sup>1,9-57,59-117</sup>**

Sling category	Studies	Summary estimate of incidence (95% CI)	Events	Total n	Range of AE proportions across studies
Dyspareunia					
Retropubic	2	0.00% (0.01–1.64%)	0	488	0.00–0.00%
Obturator	6	0.16% (0.02–1.14%)	1	624	0.00–0.40%
Minisling	11	0.74% (0.40–1.2%)	19	1809	0.00–6.49%
Pubovaginal	5	0.99% (0.39–1.9%)	8	696	0.00–2.63%

Similarly, in the AUA 2012 update to the SUI Guidelines, pain and sexual dysfunction were higher with the Burch and autologous sling than the midurethral sling:

**SUI Guideline Update Panel**  
**Complications:**  
**NO Prolapse:**

	Burch Suspension			Autologous fascia without Bone Anchors			Synthetic at Midurethra		
	G/P	Med	CI (2.5 - 97.5)%	G/P	Med	CI (2.5 - 97.5)%	G/P	Med	CI (2.5 - 97.5)%
<b>Subjective Complications</b>									
Pain	6/756	6%	(3 - 12)%	3/63	10%	(1 - 35)%	2/512	1%	(0 - 3)%
Sexual Dysfunction	5/801	3%	(2 - 4)%	4/105	8%	(3 - 16)%	1/62	0%	(0 - 4)%

The Urinary Incontinence Treatment Network conducted a large, multi-center randomized controlled trial of 597 women with SUI undergoing TVT compared with transobturator midurethral slings (there were 161 TVT-O patients and 137 TOT patients) and assessed sexual activity and function. (Zyczynski HM, et al. Sexual activity and function in women more than 2 years after midurethral sling placement. Am J Obstet Gynecol 2012; 207:421.e1-6. (TOMUS study)). The study participants were predominantly white (79.2%), middle-aged ( $52.9 \pm 11.0$  years), and obese (BMI  $30.3 \pm 6.7$  kg/m<sup>2</sup>).

Significant, similar improvements in sexual function were seen in both midurethral sling groups. Mean PISQ (Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire) scores increased from 32.8 at baseline to 37.6 at 6 months and 37.3 at 24 months ( $P < .0001$ ). Dyspareunia, incontinence during sex, and fear of incontinence during sex each significantly improved after surgery. Specifically, pain with intercourse was reported by 153 of 406 of sexually active women (38%) at baseline and decreased to 27% at 12 months after surgery ( $P = .003$ ). Self-reported urge incontinence and the fear that incontinence might occur during sexual activity also significantly improved by 12 months after surgery, regardless of sling route ( $P < .0001$  for both). Neither intra-operative nor postoperative complications were associated significantly with sexual activity or function. To investigate the association of synthetic mesh slings with dyspareunia, the study authors repeated the analysis on the 247 women who underwent MUS only (no concurrent procedures) and who completed baseline and 12-month assessments. The positive effect of TVT and TVT-O on dyspareunia were again seen. In this subset of women, dyspareunia decreased from 57% at baseline to 43% at 12 months after surgery ( $P = .03$ ). Preoperative urge incontinence was associated with abstinence after surgery ( $P = .02$ ). Postoperative urge incontinence was associated with diminished sexual function as measured by PISQ-12 ( $P = .047$ ), but did not affect frequency of self-reported sexual activity.

Similarly, in a 12 month study, sexual function was found to improve in women with urodynamic stress incontinence (USI) and intrinsic sphincter deficiency (ISD). A significant increase was detected in PISQ-12 score following both TVT and Monarc

insertion. This score was greater in the TVT group at 6 months but not at 12 months when compared to the Monarc group. A significant decrease in UDI-6 and IIQ-7 score was detected. Specifically, coital incontinence and fear of leakage were reduced in both groups, and no change in dyspareunia or orgasm intensity was found. (De Souza A, et al. Sexual function following retropubic TVT and transobturator Monarc sling in women with intrinsic sphincter deficiency: a multicentre prospective study. *Int Urogynecol J*. 2012 Feb;23:153-8.)

Patient satisfaction was also assessed across numerous parameters in the TOMUS trial. (Wai CY, et al. Patient Satisfaction After Midurethral Sling Surgery for Stress Urinary Incontinence. *Obstet Gynecol* 2013;121:1009–16) Both the TVT and TVT-O groups demonstrated a high level of satisfaction in patients with respect to urine leakage (retropubic 85.9% compared with transobturator 90.0%), urgency to urinate, frequency of urination, capability of physical activity, social activity, ability to engage in sexual activity, and from an emotional standpoint. A very telling point is that more than 95% of participants in both sling groups indicated that they would still choose to have the surgery or recommend it to a family member or friend if they could go back in time with the knowledge and experience they acquired after the surgery.

Other studies have shown the TVT and TVT-O to be safe and effective in overweight and obese. In a meta-analysis of seven TVT studies including 453 obese and 1186 non-obese patients, good cure rates were shown in the obese group (81%) and the non-obese group (85%). (Greer WJ, et al. Obesity and pelvic floor disorders: a

systematic review. Obstet Gynecol. 2008;112:341-9.) Although statistically significant, the difference is not clinically significant.

Outcomes of the TVT® procedure in the obese

Study	N (Obese / Nonobese)	Follow-up (months)	% Cure (Obese / Nonobese)	P value	Complications
Mukherjee et al (26), 2001	87 / 156	Not given	90 / 91.2	NS	No difference in urinary retention, operative complications
Chung et al (32), 2002	60 / 31	(12 -24)	100 / 100	NS	No difference in length of hospital stay, voiding dysfunction
Rafii et al (31), 2003	39 / 149	27 (6 - 38)	82 / 91.2	0.1	More persistent urge UI in obese (17.9% vs. 4.6%)
Lovatsis et al (28), 2003	35 / 35	(6 - 24)	88.6 / 91.4	NS	- More bladder perforations in nonobese (14 vs. 0%, $P = 0.03$ ) - Longer operative time in obese (49 vs. 35 min, $P < 0.05$ )
Skripas et al (27), 2005	31 / 52	18.5 (12 - 24)	87 / 92	0.103	More early postoperative complications in obese (48.4% vs. 38.5%, $P = 0.021$ )
Ku et al (33), 2006	45 / 240	10	84.4 / 91.6	0.173	No difference in urinary retention, persistent urgency
Hellberg et al (30), 2006	163 / 570	68.4 (24 - 96)	66.1 / 77.5	*	* Cure rates for BMI < 25 = 81%, for BMI > 35 = 52.1% ( $P = 0.0005$ )

The rate of bladder perforation was also assessed in the meta-analysis and the results did not show an increased risk in the obese patients as combined bladder perforation rates were 1.2% in the obese and 6.6% in the non-obese.

More recently, another paper showed that overweight and obese women undergoing TVT and TVT-O have good cure rates and the procedure is safe. (Osborn DJ, et al. Obesity and female stress urinary incontinence. Urology. 2013;82:759-63.) Several studies were included on this point and overall the subjective and objective cure rates were similar as can be seen in Table 1:

**Table 1.** Outcomes after midurethral sling surgery in the obese population

Author	Year	Follow-up Mo	Procedure	BMI	No. of Patients	Cure Rate	
						Subjective	Objective
Mukherjee <sup>38</sup>	2001	6	TVT	<25	58	85%	
				25-29	98	95%	
				>30	87	89%	
Rafii <sup>39</sup>	2003	(27)	TVT	20-25	86	74%	93%
				26-30	62	72%	89%
				>30	39	72%	82%
Skriapas <sup>40</sup>	2006	(18)	TVT	<30	52	92%	90%
Ku <sup>41</sup>	2006	(10)	TVT	>40	31	87%	90%
				18.5-23	81	93%	
				23-27.5	159	91%	
Hellberg <sup>36</sup>	2007	(68)	TVT	>27.5	45	84%	
				19-24	291	81%	
				>35	61	52%*	
Killingsworth <sup>42</sup>	2009	12	TVT	<25	68	81%	
				25-29.9	65	86%	
				≥30	62	82%	
Rechberger <sup>43</sup>	2010	18	TVT	<25	41	81%	
				25-29.9	80	80%	
				>30	80	68%	
			TOT	<25	43	86%	
				25-29.9	81	72%	
				>30	73	70%	
Stav <sup>44</sup>	2010	(50)	TVT	<25	371	94%	
			TOT	>25	741	80%*	
Esin <sup>45</sup>	2011	12	TOT	<25	42	96%	92%
				>30	46	91%	91%
Haverkom <sup>46</sup>	2011	(23)	TOT	<30	161	92%	
				>30	117	81%*	
Mohamad Al-Ali <sup>47</sup>	2011	12	TVT	<25	25	60%	76%
				25-30	33	61%	76%
				>30	35	49%	40%
Hwang <sup>48</sup>	2012	12	TVT	<22.9	90	94%	94%
				23-27.5	153	96%	97%
				>27.6	31	97%	97%
			TOT	<22.9	13	92%	100%
				23-27.5	33	94%	91%
Heinonen <sup>49</sup>	2013	(66)	TOT	>27.6	3	67%	67%
				<30	100	85%	
--				>30	34	84%	

While Plaintiffs' experts opine that there is an increased risk of infection with the TVT and TVT-O mesh slings, the data do not bear this out. Overall, the risk of infection with the TVT and TVT-O mesh is very low. The Ford 2015 Cochrane Review analyzed data from several registries (Collinet 2008; Dyrkorn 2010; Kuuva 2002; Koops 2005; Tamussino 2001; Tamussino 2007; Tincello 2011) involving thousands of patients and found the infection rate for retropubic slings was 0.7% and for transobturator it was 0.6%. (Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015 Jul 1;7:CD006375. PMID: 26130017).

Infections and wound complications can and do occur with any SUI surgery. The Schimpf 2014 SGS systematic review and meta-analysis reported the following wound infection rates which show that TVT and TVT-O have lower rates than the pubovaginal sling and Burch:

- Obturator 0.74%
- Retropubic 0.75%
- Pubovaginal 2.6%
- Burch 7.0%

Similarly, in the SISTER and TOMUS trials, both of which were conducted by the UITN, the authors reported wound complication rates as follows for both trials at 2 years:

<b><u>Study</u></b>	<b><u>UTIs</u></b>	<b><u>Wound Complications Requiring Surgery</u></b>	<b><u>Wound Complications Not Requiring Surgery</u></b>
Burch ( <i>Albo 2007; n=329; 2 years</i> )	32% (n=105 with 203 events)	13 events	69 events
Fascial Sling ( <i>Albo 2007; n=326; 2 years</i> )	48% (n=157 with 305 events)	11 events	71 events
TVT ( <i>Albo 2012; n=298; 2 years</i> )	17.4% (n=52 with 64 events)	11 events	6 events
TVT-O/TOT ( <i>Albo 2012; n=299; 2 years (TVT-O=161 &amp; TOT=137)</i> )	10.7% (n=32 with 35 events)	11 events	2 events

While mesh exposures were the most common wound complication in the TVT and TVT-O groups, other various wound complications occurred in the Burch and fascial sling groups:

- Wound complications requiring surgical intervention included incisional hernia (Burch, 5 patients; sling, 3), seroma or hematoma (Burch, 2; sling, 3), infection (Burch, 2; sling, 2), abscess (Burch, 1; sling, 1), and vaginal wound revision (Burch, 3; sling, 2).
- Wound complications not requiring surgical intervention included 2 sling exposures (visualization of the sling material in the vagina), incisional hernia (Burch group, 2; sling group, 1), superficial wound-edge separation (Burch, 10; sling, 5), seroma or hematoma (Burch, 13; sling, 11), infection (Burch, 31; sling, 21), and granulation tissue or stitch granulomas (Burch, 13; sling, 31).

Overall the data show that the rates of mesh exposure with TVT and TVT-O are in the 1 - 2.5% range and are manageable (Ford 2015 Cochrane Review: Retropubic 2.1% (21/1000), transobturator 2.4% (24/1000); Meta-analysis of Registries (Collinet 2008; Dyrkorn 2010; Kuuva 2002; Koops 2005; Tamussino 2001; Tamussino 2007; Tincello 2011): Retropubic 1.5%, transobturator 0.4%; Schimpf SGS 2014 Systematic review: Retropubic 1.4%, transobturator 2.2%; Novara 2008 Table 6 metaanalysis of 34 studies with >24 months follow up: TVT 1.1%.)

Studies on TVT and TVT-O also consistently report that there is a low rate of revision for voiding dysfunction, mesh exposure and other complications. As noted earlier, the metaanalysis by Novara of more than 30 TVT studies with more than 24 months follow up reported a 3.2% reoperation rate. The Ford 2015 Cochrane Review's assessment of multiple registries (n= 809 to 4281) found reoperation rates relating to

tape insertion or postoperative voiding dysfunction (POVD) from 1.6% to 2.4% for retropubic tape and 0.8% to 2.2% for transobturator tape. The Schimpf 2014 SGS systematic review and metaanalysis reported a 1.9% rate of return to the OR for erosion and 1.2% return to OR for urinary retention for retropubic slings and 2.7% and 1.1% rates for transobturator tapes.

Welk's recent analysis of Canadian databases involving 59,887 patients undergoing a SUI mesh sling reported a cumulative incidence rate for mesh revision/removal of 3.3% at 10 years follow up. (Welk B, et al. Removal or Revision of Vaginal Mesh Used for the Treatment of Stress Urinary Incontinence. JAMA Surg. 2015; 9:1-9.) These results are consistent with an analysis of data from US health maintenance organizations involving 188,454 eligible women who underwent an index sling that reported a 9-year rate of sling revision/removal of 3.7% consisting of 2.5% for mesh erosion and 1.3% for urinary retention. (Jonsson Funk M, et al. Sling revision/removal for mesh erosion and urinary retention: long-term risk and predictors. Am J Obstet Gynecol. 2013; 208:73.e1-7.).

A paper by Nguyen evaluating Kaiser Permanente data reported 2.2% of MUS patients had surgery consisting of 1.3% for voiding dysfunction or urinary retention, 0.8% for vaginal mesh erosion, 0.08% for urethral erosion, and 0.04% for pain (1/3,747). (Nguyen JN, et al. Perioperative complications and reoperations after incontinence and prolapse surgeries using prosthetic implants. Obstet Gynecol. 2012; 119:539-46.) A paper by Unger reported a 2.7% rate of reoperation (89/3,307) for slings, with revision

more common for voiding symptoms and/or urinary retention than mesh exposure. (Unger CA, et al. Indications and risk factors for midurethral sling revision. Int Urogynecol J. 2015 Jul 2 (e pub)). Like Nguyen's paper, reoperation due to vaginal pain/dyspareunia in Unger's paper was very rare overall in patients who received a sling, 7 of 3,307 patients (0.2%). Reoperation due to groin pain was a reason in 3.4% (n=3) of the 89 surgeries, which translates into a very rare overall absolute risk of 0.09% (3/3,307) of patients who received a sling.

In Laurikainen's five year RCT of TVT (n=131) versus TVT-O (n=123) noted above, complication rates were low, with no difference between groups, and none of the patients had any sign of tissue reaction, erosion, or tape protrusion at their 5-yr follow-up that included 95% assessment of enrolled patients. (Laurikainen E, et al. Five-year results of a randomized trial comparing retropubic and transobturator midurethral slings for stress incontinence. Eur Urol. 2014; 65:1109-14.) With regard to efficacy, the objective cure rate was 84.7% in the TVT group and 86.2% in the TVT-O group, subjective treatment satisfaction was 94.2% in the TVT group and 91.7% in the TVT-O group, and significant improvement was seen in all condition-specific QoL questionnaires for both groups, with no statistically significant differences between the groups.

In a 7 1/2 year study of 124 women undergoing TVT-O, objective and subjective cure rates were 81.5 % and 83.5 % with significant improvement in all KHQ domains. (Athanasίου S, et al. Seven years of objective and subjective outcomes of transobturator

(TVT-O) vaginal tape: why do tapes fail? *Int Urogynecol J.* 2014; 25:219-25.) There were no major perioperative complications. Reoperation for tape failure was low and occurred in three patients (2.4%). Only one patient (0.8 %) required tape division 3 months after surgery for voiding difficulties and one patient (0.8 %) had a midline mesh exposure diagnosed 1 year after the procedure that was excised. At the long term follow-up visit, no cases of vaginal erosions were detected and no patient reported persistent groin pain.

In the 5 year study by Serati, subjective and objective cure rates after TVT-O were 90.3% and 90.8%, and there were no long term mesh erosions or groin pain. (Serati M, et al. TVT-O for the treatment of pure urodynamic stress incontinence: efficacy, adverse effects, and prognostic factors at 5-year follow-up. *Eur Urol.* 2013; 63:872-8.) Eleven (5.8%) women reported early postoperative voiding dysfunction, but only in one case (0.5%) was TVT-O revision necessary. Vaginal erosion was recorded 12 months after TVT-O in two cases (1%) and one of these required sling removal (0.5%).

Tommaselli's recent systematic review and metaanalysis of 49 medium and long term studies showed that TVT-O was associated with a significantly lower incidence of vaginal injuries than TOT and there was no difference in persistent pain, defined as all pain reported beyond the perioperative period (>7 days after procedure), between RP-MUS and TO-MUS (2.2 % vs. 1.9 %). Persistent or chronic pain (i.e. pain persisting beyond the perioperative period or reported at the last follow-up visit) was very rare and reported by 13 patients for RP-MUS (13/3,974 = 0.3%) and 30 patients for TOMUS

(30/2,432 = 1.2%). (Tommaselli GA, et al. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. *Int Urogynecol J*. 2015; 26:1253-68.) Notably TVT and TVT-O represented the vast amount of data as they were represented in 43 of the 49 studies (Tables 1 and 2).

Overall, these data show that the TVT and TVT-O are very safe and effective based on high level studies with long follow up. The significant amount of level 1 evidence and long term data demonstrate that the TVT and the TVT-O and the macroporous Prolene polypropylene are optimal. Plaintiff's experts' claims that the mesh is cytotoxic, degrades, contracts, causes cancer and leads to an untoward inflammatory response are without support in the reliable scientific literature. The body of data on TVT and TVT-O do not demonstrate these concerns. While cytotoxicity was noted in an in vitro cell assay presented to the FDA in the 510k of TVT, the overall clinical data was also presented which did not show cytotoxicity. The clinical data since also do not demonstrate cytotoxicity or an adverse inflammatory effect, as the mesh incorporates, there is long term efficacy and low complications including wound complications as discussed earlier and below. Moreover, if the mesh was cytotoxic, it would not incorporate and there would be tissue necrosis in all of the patients implanted with TVT and TVT-O. This has not been demonstrated.

Degradation of the mesh has not been demonstrated by reliable data. While there have been reports of "surface cracking" such as that described in the Clave 2010

paper, the authors there confirm that the phenomenon which was only observable in a minority of specimens could not be demonstrated on analytical chemical testing.

Moreover, the methodology of the paper was flawed and unable to rule out that the surface cracking was not biofilm. The data do not support that any surface cracking causes clinical symptoms. To the contrary, polypropylene is a stable and well-accepted biomaterial with a history of over five decades of use in mesh implants. While plaintiffs' experts hypothesize that surface changes lead to adverse clinical outcomes, this is not supported by the extensive peer-reviewed literature related to polypropylene mesh repairs and specifically to the TVT and TVT-O devices.

Prospective studies have followed patients with implanted with TVT and TVT-O for 5-17 years and show excellent durability and safety with the use of the macroporous Prolene polypropylene sling. (AUGS-SUFU FAQs by Providers on Mid-urethral Slings for SUI 2014; Tommaselli GA, et al. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. *Int Urogynecol J.* 2015; 26:1253-68; Ford AA, et al. Mid-urethral sling operations for stress urinary incontinence in women. *Cochrane Database Syst Rev.* 2015 Jul 1;7:CD006375. [Epub ahead of print] PubMed PMID: 26130017; Nilsson CG, et al. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. *Int Urogynecol J.* 2013; 24:1265-69; Athanasiou S, et al. Seven years of objective and subjective outcomes of transobturator (TVT-O) vaginal tape: why do tapes fail? *Int Urogynecol J.* 2014; 25:219-25.)

Numerous data cited in my report show that the macroporous Prolene polypropylene tape is well tolerated and provides lasting efficacy for SUI. For example, in the 10 year study by Svenningsen which evaluated 483 women at a median duration of 129 months follow-up, there was a 90% objective cure rate, only 2.3 % of the women had undergone repeat SUI surgery, and the total number of exposures was 4 (0.8 %) for the whole 10-year period, with only 1 case of asymptomatic mesh exposure (0.2%) found at the 10-year follow-up. (Svenningsen R, et al. Long-term follow-up of the retropubic tension-free vaginal tape procedure. *Int Urogynecol J*. 2013; 24:1271-78.)

In the 10 year study by Serati, the 10 year subjective, objective, and urodynamic cure rates were 89.7%, 93.1%, and 91.4%, no patient required tape release or section during the 10 year follow-up, and there were no vaginal, bladder, or urethral erosion, or de novo dyspareunia noted. (Serati M, et al. Tension-free vaginal tape for the treatment of urodynamic stress incontinence: efficacy and adverse effects at 10-year follow-up. *Eur Urol*. 2012; 61:939-46). More recently, the 13 year study results by Serati were published and showed excellent efficacy and safety. (Serati M, et al. TVT for the treatment of urodynamic stress incontinence: Efficacy and adverse effects at 13-year follow-up. *Neurourol Urodyn*. 2015 Oct 19. doi: 10.1002/nau.22914. [Epub ahead of print]) The 13 year subjective, objective, and urodynamic cure rates were 85.5%, 90.9%, and 89.1%. Additionally, no patient required tape release or section during the 13 year follow-up, and there were no vaginal, bladder, or urethral erosion, or de novo dyspareunia noted.

In the 10.5 year study by Heinonen, objective and subjective cure rates were 90% and 78% and only three patients (2.3%) had adverse events at 1–11 years postoperatively. (Heinonen P, et al. Tension-free vaginal tape procedure without preoperative urodynamic examination: long-term outcome. *Int J Urol*. 2012; 19:1003-9.) Two patients with retention and pain had the tape cut without any further problems and the other patient had recurrent urinary tract infections and dysuria as a result of tape erosion into the bladder.

In the 10 year study by Aigmueller, only 2.8% of patients (4/141) had repeat incontinence surgery and there were 2 mesh related reoperations (1.4%) due to mesh erosion. (Aigmueller T, et al. Ten-year follow-up after the tension-free vaginal tape procedure. *Am J Obstet Gynecol*. 2011; 205:496.e1-5.) In the study by Olsson with a median 138 month follow up, there was only one case (0.8%, 1/124) of wound healing which occurred two months post-operatively, three cases of early tape release (2.4%) for retention, and there were no late adverse effect including erosion of tape rejection at long term follow up. (Olsson I, et al. Long-term efficacy of the tension-free vaginal tape procedure for the treatment of urinary incontinence: a retrospective follow-up 11.5 years post-operatively. *Int Urogynecol J*. 2010; 21:679-83). These data are inconsistent with Plaintiff's experts' theories.

There are no reliable scientific data that not show a risk of cancer and reliance by Plaintiff's experts on MSDS sheets and data in rats while attempting to extrapolate to humans is unreliable and improper methodology. (Moalli P, et al. Polypropylene mesh:

evidence for lack of carcinogenicity. Int Urogynecol J. 2014; 25:573-6; King AB, Goldman HB. Current controversies regarding oncologic risk associated with polypropylene midurethral slings. Curr Urol Rep. 2014; 15:453.) There are no epidemiologic data which shows that there is a statistically significant risk compared to the background rate of malignancy. King reported a series of 2,361 polypropylene midurethral slings with a follow-up extending up to 122.3 months and the rate of cancer formation was 0.0 % and no sarcomas were reported. (King AB, et al. Is there an association between polypropylene midurethral slings and malignancy? Urology 2014; 84:789-92). As observed by AUGS and SUFU in their 2014 Frequently Asked Questions by Providers on MUS for SUI:

Tumors related to the implantation of surgical grade polypropylene for mid-urethral slings in humans have never been reported. There is no compelling evidence supporting human malignant transformation related to polypropylene despite the millions of individuals implanted with various forms of this material spanning well over a half century world-wide. The possibility that biomaterial prosthetic devices could cause tumors or promote tumor growth has been the focus of extensive research by both clinicians and biomaterial researchers. (McGregor, D.B., et al., Evaluation of the carcinogenic risks to humans associated with surgical implants and other foreign bodies - a report of an IARC Monographs Programme Meeting. International Agency for Research on Cancer. Eur J Cancer, 2000. 36(3): p. 307-13; Ratner, B.D., et al., eds. Biomaterials Science: An Introduction to Materials in Medicine - 3rd Edition. 2013, Academic Press: Waltham, MA.) It is known that tumor formation related to

biomaterials in animals is largely dependent on the physical, not the chemical configuration of the implant, with smooth large surface areas (discs and thin sheets) being potentially carcinogenic, and irregular disrupted surfaces (e.g. those that contain pores as in meshes) lacking carcinogenicity (Ratner, B.D., et al., eds. Biomaterials Science: An Introduction to Materials in Medicine - 3rd Edition. 2013, Academic Press: Waltham, MA.; Oppenheimer, B.S., et al., The latent period in carcinogenesis by plastics in rats and its relation to the presarcomatous stage. Cancer, 1958. 11(1): p. 204-13.).

Most recently, a study of 2,474 patients who underwent polypropylene sling placement and followed for a median of 5 years demonstrated that there is no association between polypropylene and cancer or sarcoma in humans. (Linder 2016 ). Only 2 malignancies (0.08 %) occurred after sling placement while there 49 cancer diagnoses which preexisted the sling placement, demonstrating a much higher background rate of cancer. No cases were seen in patients with more than 10 years follow up. No data have shown a statistically significant higher rate of sarcoma formation or cancer compared to background rates in women.

Overall the data show that the TVT and TVT-O are safe and effective. The TVT was developed to provide for a less invasive, less morbid SUI surgery that could be performed in an ambulatory manner. The data show that it is highly effective in the long term and has less complications and in particular serious complications and voiding difficulties than the Burch colposuspension and autologous sling. The TVT-O followed in its design and it demonstrates high levels of efficacy along with an even lower rate of

serious complications. Like the TVT, the TVT-O is minimally invasive, less morbid and has less complications than the Burch colposuspension and autologous sling. Overall TVT and TVT-O lead to shorter operating times, shorter hospital stay, reduced operative pain, reduced voiding dysfunction, and a quicker recovery. TVT and TVT-O are the most studied devices for SUI surgery and they have been studied more than the Burch colposuspension and autologous sling. The macroporous Prolene polypropylene tape in TVT and TVT-O is the optimal material for SUI surgery. It is biocompatible and has demonstrated tolerability. Complications are low and manageable. While mesh exposure can occur, other wound complications occur in a significant portion of patients undergoing the Burch colposuspension and autologous sling. The design of both devices was and is state of the art and the vast majority of pelvic surgeons in the US and abroad prefer the polypropylene midurethral sling over the Burch colposuspension and autologous sling. TVT and TVT-O have been assessed in numerous high level data including RCTs, metaanalyses, systematic reviews and professional society guidelines, bulletins and position statements which rely on the highest levels of evidence. TVT and TVT-O have been found to be safe and effective in the short and long term, with low morbidity and complications, and having great utility and usefulness to surgeons and patients. Overall reoperation rates are low and complications are manageable.

Potential risks of SUI surgery are well described to surgeons during training, in medical textbooks, and in the medical literature, and are well known elemental risks that surgeons would be aware of. The same is true for the tensioning of sutures as well as slings, whether made of synthetic or animal or native tissue, and the potential

complications such as voiding dysfunction. Pain, pelvic pain, and dyspareunia can occur with any SUI surgery and vaginal surgery, are well known and described in the literature, as well as taught to surgeons in their education and training. Dyspareunia and sexual dysfunction that preexists in women can also be cured or improve following TVT or TVT-O placement. Mesh exposure/erosion is the only unique risk when using the TVT and TVT-O and it is uncommon and can be easily treated in the majority of cases. Suture and sling erosion and wound complications can occur with non-TVT/TVT-O SUI surgeries. These risks would be known by surgeons of the type to perform SUI surgery and would be obvious based on basic SUI surgical principles and knowledge as well as observation of the surgical instruments involved. The TVT and TVT-O are not defective in their design and from my perspective as a surgeon, the risks are adequately described in the IFU and professional education materials, and would be known by pelvic surgeons and obvious.

A handwritten signature in black ink, appearing to read 'C. Pramudji', written over a horizontal line.

Christina Pramudji, M.D.

February 26, 2016

# Exhibit C

### **EXPERT REPORT OF CHRISTINA PRAMUDJI, M.D.**

The following is a summary of my qualifications and my opinions in this case as of the date of this report. This report is based on the information I have now. To the extent I receive additional information between now and the time of the trial, I may form additional opinions or some of my opinions may be modified.

All of my opinions are held to a reasonable degree of medical and scientific certainty and probability. Below is a summary of my general opinions as set forth in more detail in my report. All of my opinions are based on my education, training, and clinical experience, the medical literature and materials that I have reviewed, my discussions with colleagues, my research and review of the medical records and deposition testimony provided to me in this case, and from the perspective of a board-certified urologist with subspecialty board certification in Pelvic Floor Medicine and Reconstructive Surgery.

- Pelvic organ prolapse and incontinence are common conditions in women. They commonly co-occur in women. There are many risk factors for prolapse and incontinence.
- Pelvic organ prolapse and incontinence can be very distressing and burdensome to women and can cause adverse effects on women physically, mentally, and socially. Both can adversely affect quality of life and relationships.
- Pelvic organ prolapse is usually treated with a pessary, a non-surgical option, or with surgery. Conservative efforts to treat prolapse with a pessary may not

be a suitable option for some women and they may not always provide relief.

Many women who try a pessary will discontinue the therapy.

- Surgery for prolapse is common, frequently involves various prolapse procedures, and is also frequently combined with other procedures such as hysterectomy and incontinence surgery.
- Pelvic floor reconstruction surgery for prolapse can be and is frequently categorized by route into the abdominal or vaginal approach, with the vaginal route most often employed. Native tissue repairs are most often done vaginally. Examples include colporrhaphy, paravaginal repair, and sacrospinous or uterosacral ligament suspensions. Surgical mesh is employed for both the abdominal (sacrocolpopexy) and vaginal approaches. The abdominal approach is more morbid and extensive, leading to higher significant complication rates, blood loss, postoperative discomfort, length of hospital stay and cost. Pelvic floor reconstruction surgery for prolapse can also be further divided by the type of prolapse, such as cystocele, rectocele, vault prolapse, or a combination of these, and as stated above multiple procedures are sometimes employed to treat site-specific defects.
- Synthetic mesh has been used to treat prolapse since the 1960s. This is because the various native tissue repairs are associated with higher rates of failure and surgeons have continually sought better options for their armamentarium. Over the past 50 years, pelvic floor surgeons have employed surgical mesh for abdominal sacrocolpopexy and for vaginal procedures, such

as the use of free cut mesh, transvaginal mesh kits or the reinforcement of colporrhaphy with mesh.

- Mesh made of monofilament, large pore polypropylene, like Gynemesh PS which is also used in the Prolift and Prosima devices and sacrocolpopexy, has been most commonly used and is the standard for both the abdominal and vaginal approaches to pelvic organ prolapse repair. The mesh is made of the same polypropylene as the Prolene suture, which can be used in vaginal vault prolapse procedures like the sacrospinous or uterosacral ligament suspension surgeries. The clinical data shows that the monofilament, large pore polypropylene like Gynemesh PS allows for adequate tissue ingrowth and is not associated with a significantly increased risk of infection over that generally associated with prolapse surgery and vaginal surgery, which is consistent with my clinical experience in hundreds of women. The data in women does not support that Gynemesh PS degrades, as reoperation rates for recurrence are low, cure rates and satisfaction is high, and complication rates are not consistent with degradation or that if it did degrade, it would have a clinically significant effect, and I have not seen evidence of mesh degradation in my clinical practice.
- Gynemesh PS has been the most studied mesh in pelvic reconstructive surgery. There are numerous randomized controlled trials and over 100 studies which demonstrate that Gynemesh PS, when used itself or in the Prolift and Prosima devices, is effective, safe and useful. No other mesh has

been studied nearly to the degree of Gynemesh PS and in this regard it surpasses all industry standards and is state of the art. It has proven efficacy and safety in both the abdominal and vaginal applications for treating POP.

- While Plaintiffs' experts posit that there are safer or better meshes like PVDF, Dynamesh, and Vypro, these meshes have not been demonstrated to be more efficacious or safer based on the reliable scientific literature nor have they been studied in the prolapse application like Gynemesh PS. As later discussed, Vypro when studied for prolapse was found to be not well tolerated. Ultrapro has been referenced as a safer alternative. However, studies of it show similar rates of mesh exposure and dyspareunia and change in sexual function as Gynemesh PS and Prolift and it has not been demonstrated to be more efficacious.
- Gynemesh PS and Prolift have a positive benefit-to-risk profile. Overall, the Gynemesh PS and Prolift provide better anatomic support than native tissue repairs and subjective satisfaction is very high, as will be discussed. Improvements in quality of life following are also frequently seen and reported in the medical literature and more recent data show improvements in quality of life that are statistically significantly higher than native tissue repair. The Prolift is minimally invasive compared to the abdominal sacrocolpopexy and less morbid.
- Prosima, which also uses Gynemesh PS, has a positive benefit-to-risk profile. Overall, the Prosima provides effective treatment of anatomic defects and

subjective satisfaction with Proxima is very high, as will be discussed. Improvements in quality of life following Proxima are frequently seen and reported in the medical literature. The Proxima is minimally invasive compared to the abdominal sacrocolpopexy and less morbid. It is also potentially less invasive than trocar based mesh kits. It is indicated for stage 2 and 3 prolapse.

- All surgeries to treat pelvic organ prolapse have risks. Like Gynemesh PS, Prolift and Proxima, other prolapse and vaginal surgeries are performed in the pelvis and utilize surgical instruments, like trocars, Stamey needles, Capio needle holders, and other needle holders, in the surgical field. Potential risks of operating in this area are well described to surgeons during training, in medical textbooks, and in the medical literature, and are well-known risks. The same is true for the tensioning of sutures, grafts, and mesh whether made of synthetic, animal or native tissue, and the potential complications such as contraction of the scar tissue or pain. Tissue contraction, pain, pelvic pain, and dyspareunia can occur with any incontinence, prolapse surgery and vaginal surgery, such as concomitant posterior colporrhaphy, native tissue vault suspensions, hysterectomy and lysis of adhesions. These risks are well known and described in the literature, as well as taught to surgeons in their education and training. The clinical data do not show a statistically significant higher risk of de novo dyspareunia, de novo pelvic or vaginal pain, or change in sexual

function, or change in vaginal length with Gynemesh PS, Prolift or Prosima compared to native tissue prolapse repair.

- Mesh exposure/erosion is the only unique risk when using Gynemesh PS and synthetic mesh, and in the case of Gynemesh PS it can be treated conservatively or easily treated in an outpatient or inpatient procedure in the majority of cases. Suture and graft erosion and other wound complications can occur with non-mesh prolapse surgeries at similar and higher rates.
- Gynemesh PS, Prolift and Prosima are not defective in its design, and from my perspective as a pelvic floor reconstructive surgeon, the devices have utility and provide a durable repair. Moreover, the risks with Gynemesh PS, Prolift and Prosima are adequately described in the IFU and professional education materials. The Patient Brochures also provides adequate information to a lay person to discuss the potential options and the device with her surgeon. It is not meant to replace the surgeon-to-patient dialogue and consenting process. The Professional Education, which is recommended and incorporated into the IFU, is industry leading and above and beyond the standard of care. Professional education discusses implantation, complications and complication management as well.

## **I. BACKGROUND, TRAINING AND EXPERIENCE**

I am a board-certified urologist, with a subspecialty board certification of Pelvic Floor Medicine and Reconstructive Surgery. I received my M.D. degree from the University of Alabama School of Medicine in Birmingham in 1996. I then completed a general surgery and urology residency at Baylor College of Medicine in Houston, Texas, where I received extensive training in pelvic floor medicine and surgery. During this training I performed various surgeries to treat urinary incontinence and other pelvic and urologic conditions and disorders. Since then I have been in private practice for over 13 years and the focus of my practice is female urology and pelvic floor medicine.

I have vast experience with prolapse surgery having performed well over 1000 surgeries. I have used tailored Gynemesh PS as well as about 450 Prolift surgeries, 75 surgeries with Proxima, numerous other transvaginal mesh repairs for prolapse, native tissue repairs and hundreds of abdominal sacrocolpopexies including open and robotic sacrocolpopexies with mesh including Gynemesh PS. I was trained on the Prolift, Proxima, and Ethicon prolapse devices and was a proctor teaching them to surgeons across numerous states as well as at national conferences such as the AUA. I have a vast experience with mid-urethral slings, having performed over 1,000 sling procedures from various manufacturers and of various approaches. I am very familiar with the Ethicon TVT and TVT-O devices, having been trained in their use and having surgically placed them in hundreds of procedures. I have been a consultant for Ethicon and Boston Scientific in sling development. I also have extensive mesh experience in over 600 cases and have

managed mesh complications, as well. My urologic practice is dedicated solely to female urology, pelvic medicine, and reconstructive surgery. A copy of my curriculum vitae, which details my training, education and experience, is attached as **Exhibit "A"** to this report. A list of my publications is also set forth in my CV.

## **II. CHARGES AND TESTIMONIAL HISTORY**

For my work in this case, I am charging \$600 an hour for time spent reviewing and preparing. I charge \$700 an hour for deposition or court testimony. In the past four years, I have given testimony as an expert in the following: Connie & Kevin Schubert v. Freeman Health System et al., Jasper County Missouri Case No. 10AO-CC00219 (8/27/2013 deposition testimony), Carolyn Lewis v. Johnson & Johnson, et al., Case No.: 2:12-cv-04301 (1/10/2014 deposition testimony), Huskey/Edwards v. Johnson & Johnson, et al., (4/11/2014 deposition testimony; Sept. 2014 trial testimony), and Bellew v. Johnson & Johnson, et al., (9/17/2014 deposition testimony).

## **III. MATERIALS REVIEWED**

In this case, I have reviewed the medical literature, the Gynemesh PS, Prolift and Prosima IFUs, the Prolift Surgical Technique Guide, Prolift Surgeon's Resource Monograph, the devices' Patient Brochures, as well as the professional education materials including PowerPoint presentations, anatomy animations, and surgical videos used by Ethicon relating to Gynemesh PS, Prolift and Prosima. I have reviewed the

expert reports submitted by the plaintiffs and materials cited by Plaintiffs' experts.

Through my training, clinical and surgical experience, professional activities including CME and conference attendance, my lecturing and professional education to other pelvic floor surgeons, and my review of the literature, I am familiar with pelvic organ prolapse, the treatment of prolapse, Gynemesh PS, Prolift, Prosima and other vaginal and abdominal prolapse surgeries, other vaginal surgeries such as hysterectomy, the use of mesh for prolapse and incontinence, the development of Gynemesh PS, Prolift, and Prosima and the safety and effectiveness of prolapse surgery including the use of Gynemesh PS, Prolift, and Prosima devices. Through these means I am also familiar with urinary incontinence, the treatment of incontinence, and the medical literature relating to incontinence, including the TVT and TVT-O devices. In preparation for my testimony, I have reviewed some of that literature, as set out in **Exhibit "B."** Exhibits that will be used to support my findings and opinions, as well as documents that I have reviewed, are identified above, cited in my report, and listed in **Exhibit "B"** as well. These materials, in addition to my personal experience, knowledge, training, and education, have informed the opinions referenced above and which follow as well.

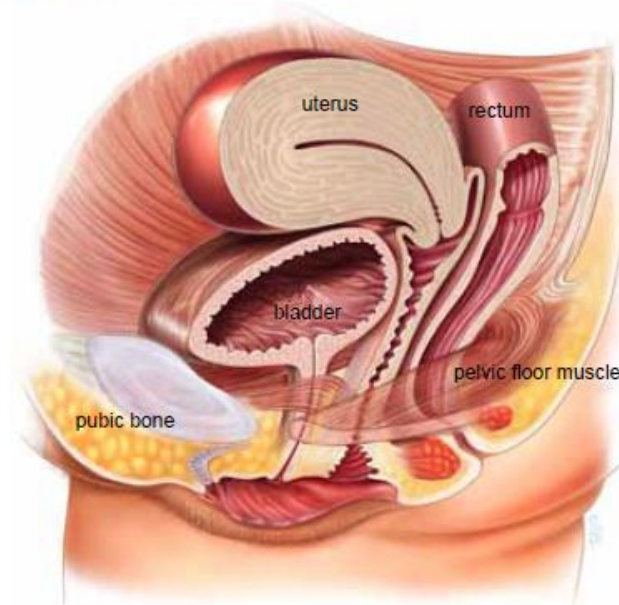
#### **IV. OPINIONS**

My conclusions and opinions are based in the practice of evidence-based medicine. As stated above, I hold all opinions set forth in this report to a reasonable degree of medical and scientific certainty and probability.

##### **A. Pelvic Organ Prolapse - Background**

Pelvic organ prolapse (POP) is the abnormal descent (dropping) of organs such as the bladder or rectum into the vagina. POP occurs due to damage and failure of the support structures in the pelvis which hold the organs in their proper anatomic position. Risk factors for POP include parity, vaginal birth, advancing age, menopause, increased body mass index (BMI) / obesity, chronic straining, smoking, chronic cough, and heavy lifting. Prior pelvic surgery such as hysterectomy also increases the risk of POP.

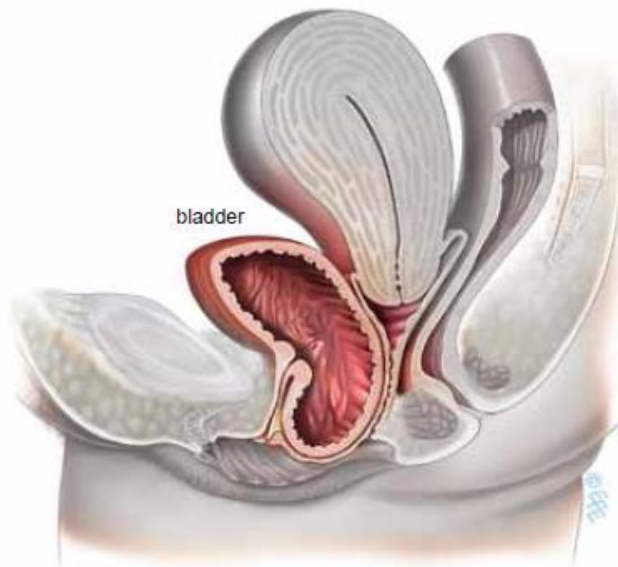
*Normal anatomy, no prolapse*



Prolapse of the Anterior compartment

This is the most common type of prolapse, and involves the bladder and / or urethra bulging into the vagina. Your doctor may refer to it as cystocele or cysto-urethrocele.

*Anterior Compartment prolapse*



IUGA 2011, Pelvic Organ Prolapse - A Guide for Women

Pelvic organ prolapse is common and is seen on examination in 40% to 60% of parous women (Maher Cochrane Database Syst. Rev. 2013). Symptoms of prolapse include a sensation of a bulge or protrusion from the vagina, heaviness, pelvic and back pain and aching, as well as symptoms of bladder, bowel or sexual dysfunction including dyspareunia. These symptoms may be directly related to the prolapsed organ, for example poor urinary stream when a cystocele is present or obstructed defecation when a rectocele is present, and they may also be independent of the prolapse, for example symptoms of overactive bladder when a cystocele is present (Maher 2013 Cochrane Review).

Cystocele, bladder prolapse, is the most common type of prolapse (Hendrix 2002 (in 16,616 women with a uterus, 34% had cystocele, 18.6% had rectocele and 14% had uterine prolapse); Fialkow 2008). In Fialkow's 10 year retrospective cohort study of 142 women, 36 recurrent cases (25%) were identified with cystocele being the most frequent element of primary (87%) and recurrent (72%) prolapse. Recurrence and reoperation are common (Clark 2003; Whiteside 2004; de Boer 2011). In the 1997 study by Olsen, 29.2% of patients had undergone at least one prior surgery for POP and/or urinary incontinence (UI) out of a group of 384 cases undergoing POP or SUI surgery (Olsen 1997). In a study of women presenting with recurrent POP symptoms, 35% of the women were found to have undergone multiple prior surgeries (Johnson 2013). In the study by Johnson, cystocele was the most common as 62% had an anterior prolapse, and 41% and 33% had posterior and apical prolapse respectively. Symptoms associated with prolapse recurrence

included 56% with incomplete emptying of bowel, 54% with urinary incontinence, 49.5% with low back pain, 42% with constipation, and 40% with dyspareunia (Johnson 2013).

#### **B. Pelvic Organ Prolapse – Treatment**

Surgery for prolapse is common, frequently involves various prolapse procedures, and is also frequently combined with other procedures such as hysterectomy and incontinence surgery. One approach to prolapse surgery is colpocleisis, an obliterative surgery. It is reserved for women who are older and/or those who do not wish to engage in vaginal intercourse.

Pelvic floor reconstruction surgery for prolapse can be and is frequently categorized by route into the abdominal or vaginal approach, with the vaginal route most often employed. Native tissue repairs are most often done vaginally. Examples include anterior and posterior colporrhaphy, paravaginal repair, and sacrospinous or uterosacral ligament suspensions. Surgical mesh is employed for both the abdominal (sacrocolpopexy) and vaginal approaches. Pelvic floor reconstruction surgery for prolapse can also be further divided by the type of prolapse, such as cystocele, rectocele, vault prolapse, or a combination of these, and as stated above multiple procedures are sometimes employed to treat site-specific defects.

Repair using native tissue for anterior colporrhaphy has high rates of recurrence, with 30–60 % failure rates (Maher 2011; Jia 2010). Jia performed a systematic review of

the efficacy and safety of mesh for anterior repair and found that mesh augmentation significantly reduced recurrence compared with traditional anterior colporrhaphy (76.9 % vs. 71.2 % cure rate, respectively).

Weber and colleagues conducted a three arm randomized controlled trial (RCT) and found significant recurrence rates -- 70% in the standard anterior colporrhaphy group failed to have satisfactory or optimal anatomic results, compared with 58% in the standard plus mesh group and 54% in the ultralateral anterior colporrhaphy group (Weber 2001). Notably, this was one of the first RCTs for a procedure that had been performed for almost 100 years. As was standard in the field, surgeons used various POP surgeries for decades relying on smaller cohort studies and their clinical experience.

Whiteside and colleagues evaluated a group of women including those in the study by Weber, undergoing prolapse and incontinence surgery and found 58% had recurrent prolapse (defined as  $\geq$  stage II for the POPQ) (Whiteside 2004). This study is also instructive in regards to the point of follow up as only 49% of the eligible women were assessed by the authors at 1 year.

Synthetic mesh has been used to treat prolapse since the 1960s (Lane 1962). Benson and colleagues conducted one of the first RCTs comparing the abdominal sacrocolpopexy and sacrospinous ligament fixation surgery (Benson 1996). Similar to the above, these procedures had been performed for decades without "level 1" RCT support. At a mean follow up of 2.5 years, surgical effectiveness was optimal (defined as remaining asymptomatic, the vaginal apex was supported above the levator plate, and no protrusion

of any vaginal tissue beyond the hymen) in 29% of the vaginal group and 58% of the abdominal group and was unsatisfactory leading to reoperation in 33% of the vaginal group and 16% of the abdominal group (Benson 1996). Sand and colleagues conducted a RCT in 161 women who underwent anterior colporrhaphy or anterior colporrhaphy with polyglactin mesh and found a 43% failure rate in the anterior colporrhaphy group which was statistically significantly higher than the 25% in the mesh augmentation group (Sand 2001). Hiltunen and colleagues also found a statistically significant decreased risk of recurrent stage 2 or greater anterior prolapse when comparing anterior colporrhaphy reinforced with Parietene light polypropylene mesh compared to anterior colporrhaphy alone (6.7% versus 38.5%) (Hiltunen 2007).

There are risks with all surgeries. All POP and vaginal surgeries have potential risks (Diwadkar 2009; Dietz & Maher 2013). All surgical procedures to treat POP can fail. All surgical procedures have some degree of pain and discomfort. All surgical procedures to treat POP may require reoperation for failure or to treat complications. Urologists, Ob/Gyns and urogynecologists are trained on the risks of these surgeries in residency and fellowship. Mesh exposure/erosion is the only unique complication of the use of Gynemesh PS, Prolift and Proxima as compared to other POP surgeries. Moreover, many POP surgeries such as SSLF, USLS, paravaginal repair, and sacrocolpopexy rely on the use of permanent sutures, which can also lead to erosion and granulation tissue (Sokol 2012 (15% suture erosion in native tissue prolapse repair arm of Prolift RCT); Toglia 2008 (36% suture-related complications at a mean time of 18.9 months postoperatively and a 25% rate of suture removal with SSLS); Yazdany 2010 (44.6% suture related complications

including 36.1% rate of suture erosion with USLS); Svabik 2014 (15% granulation tissue rate in SSLF arm of Prolift RCT); Barber 2014 OPTIMAL trial (At 6-24 months follow up in a RCT of USLS versus SSLF, there were 19.1% granulation tissue and 15.4% suture erosion rates for the USLS arm versus 14% granulation tissue and 17.2% suture erosion rates for the SSLF arm)).

Pain, pelvic pain and dyspareunia can occur with all POP surgeries (ACOG 2011 Committee Opinion 513; AUA 2011 Position Statement on the use of vaginal mesh for the repair of pelvic organ prolapse; Lowman 2008; Francis 1961). All POP surgeries have a risk of organ damage, nerve damage, de novo SUI or urge incontinence, de novo detrusor overactivity, postoperative urinary retention, incomplete bladder emptying, abscess, infection, UTI, wound infections, bleeding, fistula, scarring and tissue contraction leading to pain, dyspareunia, vaginal shortening or vaginal tightening, and reoperation for failure or to treat complications. Sacrocolpopexy can also lead to significant hemorrhage of the sacral vessels, ileus, DVT and PE, and longer anesthesia times also lead to higher risk. Additionally recovery is longer with an abdominal incision, as well as the attendant wound complications like seroma, herniation and dehiscence. Knowledge of these risks is a basic part of female pelvic surgery training and from my standpoint as a medical doctor, these risks do not need to be incorporated into the Gynemesh PS, Prolift or Prosima IFUs.

### **C. Gynemesh PS / Prolift**

Over the past 50 years, pelvic floor surgeons have employed surgical mesh for abdominal sacrocolpopexy and for vaginal procedures, such as the use of free cut mesh, transvaginal mesh kits or the reinforcement of colporrhaphy with mesh. This is because the various native tissue repairs are associated with higher rates of failure and surgeons have continually sought better options for their armamentarium. Over time surgeons began to explore the vaginal route of mesh repair because the abdominal approach is more morbid and extensive, leading to higher significant complication rates, blood loss, postoperative discomfort, length of hospital stay and cost.

The development of what would become Prolift followed this course. Early studies with polypropylene and Gynemesh PS showed good efficacy and an acceptable safety profile (Julian 1996; Migliari 2000; Berrocal 2004; Lucente 2004). Nicita sutured polypropylene mesh to the anterior aspect of the arcus tendineus fascia pelvis (ATFP) to treat anterior prolapse and found a 7% recurrence at two years (Nicita 1998). A case of mesh exposure and dyspareunia was treated with trimming the mesh and vaginal closure. De Tayrac and colleagues used Gynemesh tension-free with the lateral extensions of the mesh in contact with the ATFP and anchored with a transobturator approach (De Tayrac 2002). Anatomic success was 98% and mesh exposure was found in 8.3% after 18 months follow-up. The approaches and shapes of the mesh used to treat prolapse varied greatly and by surgeon. As a result, it was difficult to compare the results of one technique to the next.

In 2000, a group of French surgeons began investigating a standardized way to place a standardized shaped mesh (Berrocal 2004). Numerous studies had been done evaluating various types of mesh and routes of placement. The surgeons ultimately chose Gynemesh PS as the mesh to use for TVM because of its monofilament, large pore (Amid type 1) polypropylene properties. They chose routes to the ATRP and SSL as these had been employed previously for prolapse repair. Thus, surgeons were familiar with surgeries that targeted these areas of placement, such as the SSLF, paravaginal repair, posterior IVS, and transobturator midurethral slings. Cosson and colleagues reported on a group of 687 women implanted with TVM in a retrospective study beginning in 2002 (Cosson 2005). Intra-operative complications occurred in 1.3% consisting of hemorrhage, bladder and rectal injuries. Short-term postoperative complications occurred in 2.5%, of which 1.3% required surgical treatment. There was a rate of 0.15% for perineal cellulitis, vesicovaginal or rectovaginal fistulas. Perineal abscess occurred in 0.3%. Surgically treated granuloma formation or vaginal erosion occurred in 6.7%. The authors noted that the higher incidence reported at the beginning of the study was subsequently decreased owing to technical improvements, consisting of short incisions in the vagina and avoiding simultaneous hysterectomy. This potential increased risk was echoed in the Prolift Surgical Technique Guide which accompanied the IFU and in Professional Education materials. Surgically treated mesh shrinkages occurred in 2.8%. Recurrence occurred in 5.3% and de novo SUI occurred in 5.4%.

Prolift utilizes Gynemesh PS polypropylene mesh which is precut for the surgeon's convenience for anterior, posterior or total (anterior + posterior) repair and is combined

with a guide and cannulas. The mesh is inserted through a full thickness vaginal incision. Hydrodissection may be employed to aide in the dissection. The surgeon uses palpation when passing the guide, which is covered by the cannulas, through the ATFP or the SSL. A retrieval device is used to acquire the mesh arms and pull them through the cannulas. The mesh is placed tension free with the use of the cannulas and by pushing up and in on the vagina before removal of the cannulas.

While plaintiffs' experts opines that Prolift is dangerous because it uses "blind passage" of the guide, as noted above, surgeons use palpation when passing the guide. This method of seeing with one's hands is customary in pelvic floor surgery and is employed with other pelvic floor surgeries. For instance, surgeons cannot always see when passing sutures during a SSLF. Laparoscopy involves the "blind" use of a Veress needle during insufflation and multiple trocars are employed during a LSC. And, injury to organs and vessels occurs even during open abdominal procedures. Plaintiffs' experts also take issue with the Prolift mesh being placed transvaginally in the clean contaminated environment. However, surgeons use synthetic materials frequently in clean contaminated spaces. While the abdomen is in theory a clean environment, it can become clean contaminated during sacrocolpopexy with concomitant hysterectomy due to the open vaginal cuff or if a suture is passed through the full thickness of the vaginal wall. In any event, overall there is no increased risk of infection seen in the medical literature. Overall, the RCTs and studies show no significant difference in infection rates compared to native tissue and other prolapse and vaginal surgery. The macroporous

nature of the Gynemesh PS allows for inflammatory cell infiltration to effectively reduce the risk of infection.

Contrary to plaintiffs' experts' opinions, mesh exposure is not equivalent to infection. Mesh exposure is instead a wound complication and wound complications are seen with all prolapse surgeries whether or not they employ a graft and whether or not the graft is synthetic or biologic (Sokol 2012 - 15% suture erosion in native tissue prolapse repair arm of Prolift RCT; Toglia 2008 - 36% suture-related complications at a mean time of 18.9 months postoperatively and a 25% rate of suture removal with SSLs; Yazdany 2010 - 44.6% suture related complications including 36.1% rate of suture erosion with USLS; Svabik 2014 - 15% granulation tissue rate in SSLF arm of Prolift RCT); Barber 2014 OPTIMAL trial - At 6-24 months follow up in a RCT of USLS versus SSLF, there were 19.1% granulation tissue and 15.4% suture erosion rates for the USLS arm versus 14% granulation tissue and 17.2% suture erosion rates for the SSLF arm; Abed 2011 SGS Systematic Review - 110 studies reported on erosions with an overall rate of 10.3% (synthetic 10.3%; biological 10.1%) and 16 studies reported on wound granulation for a rate of 7.8% (synthetic 6.8%; biological 9.1 %)).

Mesh exposure can occur with vaginal placement and with sacrocolpopexy (Nygaard 2013). Suture erosion can occur with any surgery using permanent sutures. In the Iglesia/Sokol Prolift versus native tissue prolapse repair RCT, there were 5 patients with mesh exposure in the Prolift arm (15%), but there were also 5 patients in the native

tissue arm that had suture erosion (15%), and overall no mesh infection was noted (Sokol 2012).

In the RCT study by Svabik, there was mesh exposure in 8% of the Prolift cases and granulation tissue leading to vaginal blood spotting was seen in 15% of the SSLF cases (Svabik 2014). Mesh infection was not reported to occur in this study. In the study by Withagen, 14 patients (16.9%) had mesh exposure, of which 9 were asymptomatic and were treated with estrogen, while the remaining 5 patients underwent excision and the exposures resolved (Withagen 2011). Again, there were no cases of mesh infection.

In Abed's systematic review, erosion/exposure rates were 10% for synthetic and biologic grafts (range 0-29.7%) and wound granulation in 7% of synthetic grafts and 9% in biologic grafts (Abed 2011). In the study by Halaska, 16 patients (20.8%) had mesh exposure (Halaska 2012). One-quarter were noted to be symptomatic. Six patients underwent resection under general anesthesia and four with local anesthesia. Six exposures resolved with local estrogen.

Overall the data on Prolift and Gynemesh PS shows that it is more effective in anatomic correction compared to native tissue repair. Numerous RCTs support this:

<b>Study</b>	<b># Patients</b>	<b>Compartment</b>	<b>Mesh Anatomic Cure</b>	<b>Native Anatomic Cure</b>	<b>P value</b>
<b>Carey 2009*</b>	139	Ant & Post	81%	65.6%	P=.07
<b>Withagen 2011</b>	194	All	90%	55%	p<.001
<b>Altman 2011</b>	389	Anterior	82%	48%	p=0.008
<b>Sokol 2012</b>	65	All	38%	30%	P=0.445
<b>Halaska 2012</b>	168	All	83.1%	60.6%	P=0.003
<b>El Nazer 2012*</b>	44	Anterior	80%	35%	P<0.05
<b>Qatawneh 2013*</b>	116	All	79%	62%	P=0.043
<b>Svabik 2014</b>	70	All	97%	35%	P<0.001
<b>DaSilveira 2014</b>	184	Anterior	86.4%	70.4%	p=0.019

\*Gynemesh PS

The recent Cochrane Review echoes this conclusion specific to anterior mesh repair and found that standard anterior repair had more anterior compartment prolapse and higher awareness of prolapse than polypropylene mesh repair (Maher 2013). An earlier systematic review and meta-analysis reached similar conclusions (Jia 2008).

Other RCTs included in Table 1 of the paper by Jacquetin and colleagues show the anatomic benefit of mesh compared to native tissue:

**Table 1** Randomised controlled trials comparing polypropylene mesh with traditional native vaginal tissue repairs

Reference	Total number patients	Follow up (months)	Compartment studied	Anatomic cure mesh (%)	Anatomic cure traditional (%)	<i>p</i>
Hiltunen et al. [9]	104	12	Anterior	93	62	<0.04
Sivaslioglu et al. [10]	90	12	Anterior	91	72	<0.05
Nieminen et al. [11]	105	24	Anterior	89	59	<0.05
Nguyen and Burchette [12]	75	12	Anterior	87	55	<0.05
Carey et al. [13]	139	12	Anterior Posterior	81	65.6	0.07
Nieminen et al. [14]	202	36	Anterior	87	59	<0.0001
Withagen et al. [15]	194	12	All	90	55	<0.001
Altman et al. [16]	389	12	Anterior	82	48	0.008
Sokol et al. [17]	65	12	All	38	30	0.45

(Jacquetin 2013)

Sanses and colleagues found no difference in apical success after Prolift (98.8%) compared with uterosacral ligament suspension (99.1%) or ASC (99.3%) (Sanses 2009). However, the average elevation of the vaginal apex was slightly lower. In contrast, in both RCTs by Halaska and Svabik noted above POP-Q point C was significantly higher postoperatively in the Prolift arm compared to SSLF.

The study by Altman and colleagues was a multicenter RCT in 389 patients comparing anterior Prolift to anterior colporrhaphy which had a composite primary endpoint of success that included anatomic cure (POP-Q Stage 0-I, no prolapse or anterior wall more than 1cm above the hymen) and subjective cure (lack of symptomatic vaginal bulge) (Altman 2011). The study showed a statistically significant difference in favor of Prolift for the composite endpoint – 60.8% success versus 34.5% for colporrhaphy ( $p<0.001$ ). Of the Prolift patients, 75.4% had no symptoms of vaginal bulge compared to 62% for the colporrhaphy group ( $p=0.008$  in favor of Prolift).

Similarly, a study comparing Gynemesh PS cut in the shape of a trapezoid to anterior colporrhaphy showed significantly better anatomic improvement for the

Gynemesh PS arm at 24 months follow up -- POP-Q was optimal in 80% with Gynemesh PS compared to only 35% in the anterior colporrhaphy arm ( $p<0.05$ ) and points Aa and Ba were significantly improved with Gynemesh PS compared to native tissue ( $p<0.01$ ). (El-Nazer 2012) Subjective symptom improvements were seen with Gynemesh PS and colporrhaphy for urinary incontinence or urgency, voiding difficulty, vaginal pressure/bulge and sexual dysfunction symptoms. However, symptom improvement was significantly better ( $p<0.05$ ) with Gynemesh PS for voiding difficulty and vaginal bulge; thus, a better functional outcome was achieved in the mesh group. The authors commented that this would reflect its beneficial effect on the patient satisfaction due to better quality of life.

Another study comparing Gynemesh PS to native tissue repair in patients with Stage 3-4 uterovaginal prolapse showed a lower rate of repeat surgery for recurrent pelvic organ prolapse with Gynemesh PS ( $p=0.03$ ) and a high rate 89% of subjective success. Additionally, a recent study showed statistically significant higher anatomic cure as well as patient Quality of Life (QoL) improvements for Total Prolift versus native tissue apical repair. (daSilveira 2014)

Consistent with these benefits seen, the other RCTs also show improvement in subjective cure assessments and improvements in quality of life following Prolift:

- A high level of satisfaction with surgery (91.5%) and improvements in symptoms and quality-of-life data were observed at 12 months compared to baseline (Carey 2009).
- Subjective improvement was seen in 81% of patients. At 12 months, significant improvements in the Urogenital Distress Inventory domains “genital prolapse,” “pain” and “overactive bladder,” and “physical functioning” of the Incontinence Impact Questionnaire were noted. Defecatory Distress Inventory domains “pain” and “incontinence” scored significantly better in the Prolift group compared with the conventional group at 12 months ( $p=0.01$  and  $p=0.05$  respectively) (Withagen 2011).
- Quality of life improved and 96.2% of patients reported a cure of bulge symptoms (Sokol 2012).
- Significant improvement was observed in the Urinary Impact Questionnaire (UIQ), the Colorectal Impact Questionnaire (CRAIQ), and the Pelvic Organs Prolapse Impact Questionnaire (POPIQ) scoring and there was less improvement of bowel symptoms (CRAIQ) in the SSLF group than in the Prolift group (Halaska 2012, table 3).
- Significantly better functional symptom improvements were seen with Gynemesh PS for voiding difficulty and vaginal pressure/bulge versus anterior colporrhaphy. Significant improvement was also seen for

symptoms of urinary incontinence or urgency and sexual dysfunction symptoms. (El-Nazer 2012, table 4)

- Improvements from baseline were seen in the scores for POPDI (Pelvic Organ Prolapse Distress Inventory), UDI (Urinary Distress Inventory) and CRADI (Colorectal Distress Inventory) questionnaires. (Svabik 2014)
- In addition to significantly better anatomic improvement, subjective outcomes as assessed by the Prolapse Quality-of-Life Questionnaire (PQoL) were significantly better for Prolift compared to native tissue prolapse repair at 1-year follow-up (DaSilveira 2014, table 5).

These studies also show low rates of reoperation for prolapse recurrence. Longer term studies with Prosima, Prolift and Gynemesh PS in the TVM studies, which utilized the same shape of mesh as Prolift and the same routes of placement, have also shown a low rate of reoperation for prolapse, good efficacy and subjective cure / quality of life improvements, and acceptable rates of complications.

Benbouzid studied Prolift in a cohort of patients with 4.5 years follow up and found no recurrence leading to reoperation and an 85% cure rate defined as POP-Q Stage 0-1 (Benbouzid 2012). No recurrences were beyond POP-Q Stage II. Mesh exposure occurred in four patients (5.3%), with two undergoing revision and two successfully treated with estrogen. The authors noted that a low mesh exposure rate was also reported after a median follow up of 38 months by de Landsheere and colleagues, which is further discussed below.

Table 5 provides additional Prolift studies for comparison and they show good efficacy rates and acceptable rates of mesh exposure, which can often be treated conservatively:

**Table 5** Results of Prolift surgery according to the previous literature

Series (reference)	No. patients	Device	Type	Mean follow up	Cure rate (anatomical)	Mesh exposure	Study design
Present series	75	Prolift	Anterior: 51 Posterior: 3 Total: 20	54 months	81.5%	5.3%	Retrospective
de Landsheere 2011 <sup>14</sup>	526	Prolift	Anterior: 48 Posterior: 103 Total: 373	38 months†	N/A	3.6%	Retrospective
Vaiyapuri 2011 <sup>16</sup>	254	Prolift	Anterior: 106 Posterior: 20 Total: 128	12 months	95.6%	11.5%	Retrospective
Milani 2011 <sup>17</sup>	127	Prolift+M	Anterior: 41 Posterior: 16 Total: 70	12 months	77.4%	10.2%	Prospective
Huang 2011 <sup>13</sup>	65	Prolift	Total: 65	24.5 months†	94%	2%	Retrospective
Wetta 2009 <sup>18</sup>	50	Prolift	Anterior: 16 Posterior: 16 Total: 18	14 months	98%	2%	Prospective
Van Raalte 2010 <sup>19</sup>	91	Prolift	Anterior: 46 Posterior: 28 Total: 23	19 months†	86.6%	0%	Prospective
Nair 2011 <sup>20</sup>	60	Prolift	Anterior: 21 Posterior: 12 Total: 27	29 months	85%	15%	Prospective
Elmer 2009 <sup>21</sup>	252	Prolift	Anterior: 121 Posterior: 68 Total: 63	12 months	80%	11%	Prospective
Hollander 2010 <sup>23</sup>	323	Prolift	Anterior: 88 Posterior: 91 Total: 144	20 months	87%	11.5%	Retrospective

†Median follow up.

Also, as a comparison, Benbouzid observed that the long-term studies published about sacrocolpopexy reported significant mesh exposure between 6 and 9% (Ross JW & Preston M. Laparoscopic sacrocolpopexy for severe vaginal vault prolapse: five-year outcome. J. Minim. Invasive Gynecol. 2005; 12:221–6; Higgs PJ, et al. Long term review of laparoscopic sacrocolpopexy. BJOG 2005; 112:1134–8).

More recently, Nygaard and colleagues published the longer term results of the NIH funded extended CARE study involving abdominal sacrocolpopexy (Nygaard 2013). Of the 322 patients enrolled in the CARE trial, 215 were available for enrollment in extended CARE and 126 (only 39% of the original cohort) were available for evaluation at 7 years after their surgery. Of these 126 women, 90 were available for both physical examination and quality-of-life interviews and the remaining women had quality-of-life telephone interviews only. The probability of mesh erosion at 6.2 years was 10.5%. Of the 23 women with mesh erosions, 15 underwent excision in the operating room (13 via the vaginal route and 2 via the abdominal route), 4 were given estrogen cream, and 4 were asymptomatic. An updated composite endpoint of failure including anatomic and subjective measures was utilized and showed failure in 48% of the patients undergoing ASC + Burch and 34% without Burch. POP-Q values had to be adjudicated in 57 instances upon discovery of several discrepant values. 5% of the study population available to be assessed had undergone surgical retreatment for prolapse recurrence. This study again highlights the difficulty in following patients in clinical studies over extended periods of time.

de Landsheere and colleagues reported on reoperation rates for a large cohort of 524 patients who had undergone Prolift with a mean follow up of 38 months. (de Landsheere 2012). Rate of reoperation for mesh-related complications was 3.6% (which included 2.5% for mesh exposure, 0.2% for mesh infection, and 0.4% for severe symptomatic mesh retraction) and prolapse recurrence was 3%. This rate of surgery for mesh exposure is comparable to the 3.2% seen in the RCT by Altman (Altman 2011).

Jacquetin and colleagues reported on the French TVM study for which 91% of the patients were available at the five year follow up (Jacquetin 2013). By five years, only 4 patients (5%) required reoperation for prolapse recurrence. Anatomic success defined as POP-Q Stage 0-1 was 79% at 5 years. When using a composite outcome (like that employed by Nygaard in the extended CARE trial discussed above) with success defined as leading edge above the hymen ( $<0$ ), no bulge symptoms and no reintervention for prolapse, the success rate was 84% at 5 years. Quality of life improvements were statistically significant and were sustained. Fourteen patients (16%) had mesh exposure with 8 resections, the majority of them occurring in the first year and none were symptomatic at 5 years. De novo dyspareunia was reported by 10% of the patients but none at the 5 year interval. This rate is in line with or lower than dyspareunia rates seen with other prolapse surgeries as further discussed below. The rate of pelvic pain at 5 years was very low and decreased compared to baseline.

Miller and colleagues reported on the US TVM study for which 78% of the patients (66/85) were available at the five year follow up (Miller 2011). By five years, only 5 patients (7.6%) required reoperation for prolapse recurrence with only 2 (3%) of these patients in the treated compartment. Overall anatomic success rate defined as POP-Q Stage 0-1 was 67% and anatomic success rates in the treated compartments was 77% at 5 years. When defined as treated side leading edge above the hymen, success rates were 89% at 5 years. Statistically significant improvements in quality-of-life and Prolapse-Specific Inventory scores were sustained over 5 years. Mesh exposure was observed in 16 of 85 patients (19%) over the 5 years and 9 required partial mesh excision. There were 3

patients with some degree of dyspareunia reported between 3 and 5 years, whereas in more patients, 8 in total, preexisting dyspareunia resolved. Representing a positive net effect on dyspareunia. Moreover, pain also improved and decreased from baseline. And, overall there was an improvement in sexual function. After a 5-year period, only 1 case of de novo dyspareunia was observed in those patients sexually active before surgery, whereas resolution of this complaint was noted in at least 8 of 12 patients with preexistent dyspareunia.

Similar results were observed by Lowman and colleagues who evaluated 129 patients undergoing Prolift (Lowman 2008). At baseline, 36.8% of sexually active women reported dyspareunia. This is a significant proportion of women with dyspareunia before surgery, but is consistent with the medical literature. The rate of de novo dyspareunia was lower than or comparable to rates with other prolapse repairs:

<b>TABLE 4</b> <b>De novo dyspareunia after prolapse surgery</b>					
	<b>ASC</b> <b>N = 224 (148)<sup>a</sup></b> <b>Handa et al<sup>21</sup></b>	<b>SSLF</b> <b>N = 287 (106)<sup>a</sup></b> <b>Maher et al<sup>6</sup></b>	<b>USS</b> <b>N = 110 (34)<sup>a</sup></b> <b>Silva et al<sup>27</sup></b>	<b>APR</b> <b>N = 165 (81)<sup>a</sup></b> <b>Weber et al<sup>18</sup></b>	<b>Prolift</b> <b>N = 129 (57)<sup>a</sup></b>
<b>Dyspareunia</b>					
Baseline (preop) dyspareunia (%)	40.5 (60/148)	Unknown	20.6 (7/34)	8.0 (6/81)	36.8 (21/57)
De novo (postop) dyspareunia (%)	14.5 (11/76)	36.1 (22/61)	25.9 (7/27)	19.0 (14/75)	16.7 (6/36)
<sup>a</sup> Number sexually active preop.					
Lowman. Does the Prolift system cause dyspareunia? Am J Obstet Gynecol 2008.					

As can be seen, the rate of de novo dyspareunia ranged between 14.5% and 36.1%. Compared to the 16.7% (n=6) de novo dyspareunia rate, 33% (n=7) of the 21 women with dyspareunia at baseline had resolution. The authors reported that 92% of those with novo dyspareunia described insertional dyspareunia or dyspareunia

throughout the act of intercourse which may be attributed to perineorrhaphy as it was reportedly routinely performed in Lowman's practice. The authors also note that alternatively the dyspareunia may be due to levator myalgia, although the numbers suggest otherwise as this was only diagnosed in 11% of patients and in any event is a treatable condition. I agree with Lowman that dyspareunia is commonly reported in reproductive-aged women, menopausal women, and especially in women with pelvic floor disorders. For example, Sobhghol and colleagues performed a cross-sectional survey of 319 women aged 15-49 years and found that 54.5% reported dyspareunia (Sobhghol 2007). This is in agreement with Dietz and Maher who observed that up to 64 % of sexually active women attending a urogynecology clinic suffer from female sexual dysfunction (Dietz & Maher 2013).

Dietz and Maher reviewed the impact of pelvic organ prolapse surgery on sexual function in connection with the 5<sup>th</sup> International Collaboration on Incontinence and found that the use of mesh is associated with neither a worsening in sexual function nor an increase in de novo dyspareunia compared with non-mesh native tissue repair:

**Table 1** Meta-analysis sexual function data from randomised controlled trials (RCT) comparing transvaginal mesh with native tissue repairs

Reference	De novo dyspareunia		Postoperative dyspareunia		Postoperative PISQ score	
	Vaginal mesh	Native tissue	Mesh	Native tissue	Mesh	Native tissue
Altman et al. [15]			8/110	2/101	33.1±6.7 35.1 (1.4)	32.2±7.2 35.0 (1.4)
Vollebregt et al. [11]	3/20	2/21				
Carey et al. [12]	5/18	5/12	12/30	13/33	Change -6.9	Change -7.8
Sivaslioglu et al. [14]	2/43	0/42				
Nguyen and Burchette [13]	2/22	4/26	2/23	2/23	33±3 34±6	32±4 33±3
Iglesia et al. [21]	1/11	3/14			31/34	32/35
Milani et al. [17]	3/37	3/29	9/53	12/51	35±5.7 34.0±6.7	31.5±7.2 34.7±5.7
Total	16/151 (10.6 %)	17/144 (11.8 %)	31/216 (14.4 %)	26/207 (12.5 %)	0.09 (-0.17, 0.36) No difference	

An evaluation of the earlier noted RCTs between Gynemesh PS and Prolift and native tissue repair showed no overall difference in de novo dyspareunia, de novo pelvic pain, de novo pain, sexual functioning by PISQ scores, change in total vaginal length and change in vaginal caliber (Carey 2007; Withagen 2011; Altman 2011; Sokol 2012; Halaska 2012; El-Nazer 2012; Svabik 2014; daSilveira 2014).

For example, in the study by Carey, there was no difference in de novo dyspareunia following surgery (Carey 2009). Dyspareunia following surgery was considered to be because of vaginal stenosis in three women in the mesh group and five women in the no mesh group. Two women underwent vaginoplasty for vaginal stenosis and both were from the no mesh group.

In the study by Sokol and Iglesia, no statistically significant differences were found between Prolift (9.1%) and the no-mesh group (21.4%) with respect to new-onset dyspareunia ( $p=0.60$ , table 4), and sexual function based on PISQ-12 improved significantly and was not different between the groups (Sokol 2012). In the study by El-Nazer, baseline rates of dyspareunia were 41.1% for Gynemesh PS and 44.4% for anterior colporrhaphy. Both groups had a majority of patients with improvement and there was no de novo dyspareunia with Gynemesh PS while the anterior colporrhaphy group had 8.3% de novo dyspareunia. (El-Nazer 2012) Overall the rates of sexual function, dyspareunia and change in total vaginal length were similar. In another recent study, dyspareunia rates at 12 months were lower for Prolift compared to native tissue prolapse repair and nonsignificant. (DaSilveira 2014)

Thus, the mesh is not the cause of dyspareunia as similar rates are seen with procedures utilizing no mesh. Instead dyspareunia is attributable to numerous things such as vaginal surgery and prolapse surgery itself, vaginal atrophy, wound healing, muscle spasms and tenderness/myalgia, partner issues, decreased estrogen and other factors. These are all well known by pelvic floor surgeons. Although plaintiffs' experts point to mesh contraction as a supposed cause of dyspareunia, this is incorrect. The mesh does not contract. Instead, during wound healing the tissues contract whether or not mesh is present. Given that there is no difference in total vaginal length or caliber compared to native tissue, contraction if it does occur is no different than that seen with native tissue.

The RCTs also do not show a significant difference in pelvic and genital pain. In the study by Withagen, pelvic pain decreased compared with baseline, and at 12 months, de novo pelvic pain was reported by 2/50 (4%) in the no mesh group and 4/53 (7.5%) in the Prolift group ( $p=0.44$ , table 3) (Withagen 2011). Also of note, dyspareunia decreased at 12 months compared with baseline, and at 12 months, de novo dyspareunia was reported by 3/29 (10%) in the no mesh group and 3/37 (8%) in the Prolift group ( $p=0.75$ , Table 3).

In the study by Halaska, no statistically significant difference in pelvic pain was seen between Prolift and SSLF (Halaska 2012, table 2). Additionally there was no difference in dyspareunia. In the study by Altman, no difference in pelvic or genital pain was observed (Altman 2011, table 4). Additionally, PISQ-12 scores modestly improved.

There was no significant difference in pain during sexual intercourse reported to occur usually or always (2% in the no mesh group and 7.3% Prolift ( $p=0.07$ )). 40% of the no-mesh group and 48% of the mesh-repair group answered that they were "usually" or "always" satisfied with their sexual relationships with their partners ( $p=0.37$ ). In another recent study, post-operative pain rates were similar, and at 12 months the rate of pain was lower for Prolift compared to native tissue prolapse repair (8.6% versus 2.3%). (DaSilveira 2014)

Overall, these data show that Gynemesh PS and Prolift are safe and effective and biocompatible. While Plaintiffs' experts posit that there are safer or better meshes like PVDF, Dynamesh, and Vypro, these meshes have not been demonstrated to be more efficacious or safer based on the reliable scientific literature nor have they been studied in the prolapse application like Gynemesh PS. Vypro when studied for prolapse was found to be not well tolerated by the TVM Group. (Jacquetin 2004 ICS) Ultrapro has been referenced as a safer alternative. However, studies of it show similar rates of mesh exposure and dyspareunia and change in sexual function as Gynemesh PS and Prolift and it has not been demonstrated to be more efficacious. (Milani 2012; Bhatia 2012; Quenemer 2014).

While the most recent Cochrane Review acknowledges with permanent polypropylene mesh like Gynemesh PS, there are lower rates of awareness of prolapse, reoperation for prolapse, and prolapse on examination than native tissue repair, with no difference in repeat surgery for incontinence and no difference in dyspareunia versus

native tissue, the absorbable meshes like Vypro and Ultrapro have not demonstrated similar results (Maher 2016 Cochrane Review).

Additionally, Plaintiff's experts' claims that the mesh is cytotoxic, degrades, significantly contracts, causes cancer and leads to an untoward inflammatory response are without support in the reliable scientific literature. While cytotoxicity was noted in an in vitro cell assay presented to the FDA in the 510k of the TVT, the overall clinical data was also presented which did not show cytotoxicity. The clinical data since also do not demonstrate cytotoxicity or an adverse inflammatory effect, as the mesh incorporates, there is long term efficacy and low complications. Moreover, if the mesh was cytotoxic, it would not incorporate and there would be tissue necrosis in all of the patients implanted, which has not been demonstrated.

Degradation of the mesh has not been demonstrated by reliable data. While there have been reports of "surface cracking" (only a few microns) such as that described in the Clave 2010 paper, the authors there confirm that the phenomenon, which was only observable in a minority of specimens, could not be demonstrated on analytical chemical testing. Moreover, the methodology of the paper was flawed and unable to rule out that the surface cracking was not biofilm and/or the effect of surgical removal of the mesh. The data do not support that any surface cracking causes clinical symptoms. To the contrary, polypropylene is a stable and well-accepted biomaterial with a history of over five decades of use in mesh implants. (AUGS SUFU FAQ to Providers 2014; Ford 2015 Cochrane Review) While plaintiffs' experts hypothesize that surface changes lead to

adverse clinical outcomes, this is not supported by the extensive peer-reviewed literature related to polypropylene mesh repairs. As noted in my General TVT report, prospective studies have followed patients with implanted with TVT and TVT-O for 5-17 years and show excellent durability and safety with the use of the macroporous Prolene polypropylene sling. (AUGS-SUFU FAQs by Providers on Mid-urethral Slings for SUI 2014; Tommaselli GA, et al. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J. 2015; 26:1253-68; Ford AA, et al. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015 Jul 1;7:CD006375. [Epub ahead of print] PubMed PMID: 26130017; Nilsson CG, et al. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. 2013; 24:1265-69).

There are no reliable scientific data that show a risk of cancer and reliance by Plaintiff's experts on MSDS sheets and data in rats while attempting to extrapolate to humans is unreliable and improper methodology. (Moalli P, et al. Polypropylene mesh: evidence for lack of carcinogenicity. Int Urogynecol J. 2014; 25:573-6; King AB, Goldman HB. Current controversies regarding oncologic risk associated with polypropylene midurethral slings. Curr Urol Rep. 2014; 15:453.) There are no epidemiologic data which shows that there is a statistically significant risk compared to the background rate of malignancy. King reported a series of 2,361 polypropylene midurethral slings with a follow-up extending up to 122.3 months and the rate of cancer formation was 0.0 % and no sarcomas were reported. (King AB, et al. Is there an association between

polypropylene midurethral slings and malignancy? Urology 2014; 84:789-92). As observed by AUGS and SUFU in their 2014 Frequently Asked Questions by Providers on MUS for SUI:

Tumors related to the implantation of surgical grade polypropylene for mid-urethral slings in humans have never been reported. There is no compelling evidence supporting human malignant transformation related to polypropylene despite the millions of individuals implanted with various forms of this material spanning well over a half century world-wide. The possibility that biomaterial prosthetic devices could cause tumors or promote tumor growth has been the focus of extensive research by both clinicians and biomaterial researchers. (McGregor, D.B., et al., Evaluation of the carcinogenic risks to humans associated with surgical implants and other foreign bodies - a report of an IARC Monographs Programme Meeting. International Agency for Research on Cancer. Eur J Cancer, 2000. 36(3): p. 307-13; Ratner, B.D., et al., eds. Biomaterials Science: An Introduction to Materials in Medicine - 3rd Edition. 2013, Academic Press: Waltham, MA.) It is known that tumor formation related to biomaterials in animals is largely dependent on the physical, not the chemical configuration of the implant, with smooth large surface areas (discs and thin sheets) being potentially carcinogenic, and irregular disrupted surfaces (e.g. those that contain pores as in meshes) lacking carcinogenicity (Ratner, B.D., et al., eds. Biomaterials Science: An Introduction to Materials in Medicine - 3rd Edition. 2013, Academic Press: Waltham, MA.; Oppenheimer, B.S., et al., The latent period in carcinogenesis by plastics in rats and its relation to the presarcomatous stage. Cancer, 1958. 11(1): p. 204-13.).

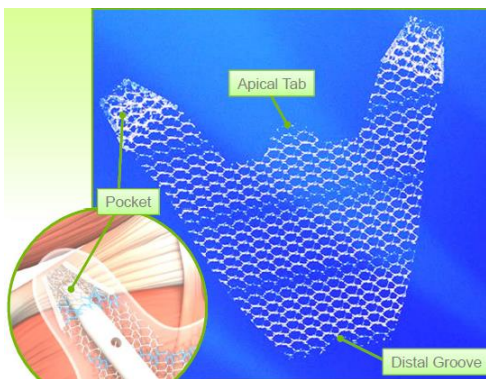
Most recently, a study of 2,474 patients who underwent polypropylene sling placement and followed for a median of 5 years demonstrated that there is no association between polypropylene and cancer or sarcoma in humans. (Linder 2016 ). Only 2 malignancies (0.08 %) occurred after sling placement while there 49 cancer diagnoses which preexisted the sling placement, demonstrating a much higher background rate of cancer. No cases were seen in patients with more than 10 years follow up. No data have shown a statistically significant higher rate of sarcoma formation or cancer compared to background rates in women.

The Ethicon Gynemesh PS and Prolift IFU, Surgical Technique Guide, Surgeons Resource Monograph and Professional education materials properly identify the steps for using Gynemesh PS and Prolift and adequately and appropriately warn surgeons of the risks associated with the device. The risks of Gynemesh PS and Prolift were appropriately identified in the IFU, were taught in surgeons' education and training, and were widely publicized in peer-reviewed literature, at professional meetings, and in the FDA 2008 and 2011 Public Health Notices. As noted above, these data were presented at conferences and also published in the peer reviewed literature, with peer reviewed papers being furnished to surgeons. Moreover, pain, erosion, scarring, contraction and dyspareunia and many other risks are warned of in the Ethicon IFU, Professional Education materials, Surgeon's Monographs, Patient Counseling materials, Patient Brochures, and other materials and are basic risks pelvic floor surgeons would be expected to know of having gone through medical school, residency and training. Any specific warnings that may be identified by Plaintiff's experts either were not necessary or were adequately included in

the Gynemesh PS and Prolift IFU and accompanying materials mentioned above, as well as in the literature and professional education materials.

#### **D. Proxima**

Proxima is a trocar-less pelvic organ prolapse device which utilizes the proven Gynemesh PS mesh combined with anterior and/or posterior inserters and a VSD/balloon device and is indicated for moderate, Stage 2-3 pelvic organ prolapse. The mesh is Y shaped and contains an apical tab and preformed pockets on the implant straps to enable placement with the inserters. The inserters are used to insert the implant straps into dissected tissue channels. The VSD is designed to provide postoperative support for the vaginal tissues after mesh placement and closure of the vaginal incisions. It is trimmed to size. The balloon is designed to replace postsurgical gauze packing and is removed the day after surgery.



Clinical research on the Prosima prototype began in 2004 and continued following FDA 510k clearance in February 2007. Prosima was not broadly launched until later in August 2010 at the joint ICS and IUGA conference in Toronto following additional clinical data.

Carey et al. reported on 95 women implanted with Gynemesh PS mesh and placement of a vaginal support device (VSD) between June 2004 and January 2005 at two centers and were studied prospectively. (Carey 2008) At 12 months, objective success was 85% and subjective success was 87%. Site specific and nature of failures were discussed in the article. Quality of life scores significantly improved at 12 months compared with baseline ( $P < 0.0001$ ). Operative and post-operative complications were discussed. There were 4 (4.2%) mesh exposures with two treated with excision and two treated with estrogen. Sexual dysfunction was reported by 58% of sexually active women preoperatively and 23% at 12 months. It was also reported that sexual dysfunction requiring further surgery was due to a mid-vaginal constriction in three women and a perineal band in one woman (Table 5). Potential benefits and risks including the risk of dyspareunia and mesh exposure of existing techniques and surgeries, as well as the subject device were discussed in the article which was peer reviewed and published for surgeons.

Cadaver studies demonstrated the accurate and safe placement of the Gynemesh PS mesh with Prosima in a cadaver model with and without pelvic organ prolapse. (Reisenauer 2009 IUGA; Reisenauer Am J Obstet Gynecol 2010).

Results of the Ethicon company sponsored Prosima multi-center study were presented at various conferences including IUGA and AUA in 2009. (Slack 2009 IUGA; Zyczynski 2009 AUA). In 2010, the one year anatomic and functional outcomes including complications from this multicenter, international prospective study of 136 patients were published and made available to surgeons. (Zyczynski et al. Am J Obstet Gynecol 2010) Overall in my opinion, the study showed improved anatomic and functional outcomes at 1 year and a low rate of complications and demonstrates that Prosima is safe, effective, and a desirable option for moderate prolapse.

Anatomic success (stage 0-1) was seen in 76.9% of patients and in 86.9% of the cases, the leading vaginal edge was above the hymen. This is where prolapse tends to become symptomatic, and is consistent with the fact that only 14% of patients reported awareness of their prolapse at 1 year, while 91% of the women reported awareness of their prolapse at baseline.

Importance in retention of the VSD for at least 21 days was noted as shortened wear of the VSD was associated with inferior anatomic support at 1 year. Curtailed wear of VSD resulted from it falling out (6 women), removal by the surgeon for suspected vaginal infection (2 women), patient discomfort (2 women), and convenience in scheduling (7 women). Median visual analog scale scores for vaginal support device awareness and discomfort at 3-4 weeks were 2.6 and 1.2, respectively (0=none to 10=worst possible). Pain at 3-4 weeks was also exceptionally low at 0.1 (0=no pain to 10=worst pain imaginable). (Table 2)

Large statistically significant improvements were seen in symptoms and Quality of Life (QoL) scores compared with baseline as recorded by Pelvic Floor Distress Inventory–20 questionnaire (PFDI-20) and the Pelvic Floor Impact Questionnaire–7 (PFIQ-7) which demonstrate positive effect of the device for the patients. (Table 4) All 3 major areas of symptoms (bowel, bladder, and prolapse) were significantly better and translated into QoL improvements. Based on Patient Global Impression of Change (PGI-C), 73.3% of patients indicated that they were “much better” and an additional 15.3% indicated that they were “a little better.” (89% of the women reported that their prolapse was “much better” or “a little better” 1 year after surgery).

Complications and complication management were also reported. Mesh exposure occurred in 12 patients (8.0%). Eight exposures resolved after partial mesh excision and 4 exposures were ongoing at 1 year. Most of the exposures were identified before or at the 6-month examinations.

In addition, in my opinion, there was a positive effect on dyspareunia and sexual function in patients treated with Prosima. 9 of 11 women who reported dyspareunia at baseline indicated resolution of dyspareunia at 1 year as compared to 3 reports of de novo dyspareunia. Moreover, twelve women (16.4%) who had not been sexually active at baseline resumed sexual intercourse without new onset dyspareunia. Additionally, statistically significant increases in Pelvic Organ Prolapse/Urinary Incontinence Sexual Function–12 (PISQ-12) scores were reported by sexually active patients (Table 4). These data demonstrate the positive effect of Prosima and show that the device does not cause

an unacceptable risk of pain with intercourse. To the contrary, these data demonstrate the beneficial characteristics of using mesh and the rates and improvements seen are better than native tissue repairs, which are known to lead to de novo dyspareunia. (Francis 1961; Karram 2013) De novo urge and stress urinary incontinence symptoms as reported on the urinary subscale of the PFDI were low and each reported by 4% of the women.

The following year, the medium term (29 month) outcomes of the Prosima study were presented at IUGA and AUGS and published in the peer reviewed literature, which again demonstrated continued efficacy and safety in moderate prolapse. (Sayer IUJ 2011) Anatomic success in this group of 110 patients who consented to follow up was 69.1% and in 84.5% of the cases, the leading vaginal edge was above the hymen. The sustained success rates reported with using the leading edge above the hymen definition (84.5%) were consistent with the patient's report of "much better" on the PGI-C global scale (82.6%, with a further 7.3% reporting their prolapse was "a little better"). When the VSD was retained for at least 21 days anatomic success at  $\geq 2$  years was 72.2% and when defined as leading edge above the hymen, it was 87.6%.

Again, large statistically significant improvements from baseline were observed and sustained over time in symptoms and QoL using the PFDI-20 and PFIQ-7 questionnaires. Pelvic symptoms and sexual function improved significantly from baseline ( $p < 0.01$ ).

The improvement in mean PISQ-12 scores reported by sexually active patients were statistically significant. Again there was a positive overall effect on dyspareunia. At baseline, dyspareunia was reported in ten sexually active patients (20%). By  $\geq 2$  years, seven of these ten women reported resolution of dyspareunia; two were not sexually active due to partner-related reasons and one patient had missing information. Two women who were sexually active at baseline reported de novo dyspareunia symptoms; in one case, the cause of dyspareunia was considered related to vulvodynia, and in the other case, the cause was considered unknown. Additionally, of the 60 non-sexually active women at baseline, 9 reported that they had resumed sexual activity by  $\geq 2$  years. Two of these patients reported dyspareunia; in both cases, the cause of dyspareunia was unknown.

In this sub-set of patients from the original study, mesh exposures were reported in 9.1% of patients (11 of 121 patients, consisting of the cohort of 110 patients and an additional 11 device run-in (DRI) cases who returned for extended follow-up which were included in safety analyses). There were 14 episodes of mesh exposure in these 11 patients, which were identified at the following times: four cases at or before 3 months post-procedure; seven at 6 months; one at 8 months post-procedure; one at 1 year; and one at 28 months. The exposed mesh was partially excised in eight patients, two of whom had second excisions. One patient who had a very small ( $<0.5$  cm) exposure identified at 6 months was not given any treatment, and this event was resolved by 1 year. Two patients were treated conservatively with topical estrogen, one of whom required further treatment with topical estrogen when a new mesh exposure was identified at

approximately 28 months. Five percent of patients reported stress urinary incontinence and 3.3% required further prolapse surgery. These data demonstrate the positive effect of Prosima and show that the device does not cause an unacceptable risk of pain with intercourse and that late exposure is uncommon as only one report of mesh exposure occurred beyond 1 year (0.8% at 28 months), which resolved following treatment with topical estrogen.

Additional studies on the Prosima device have shown that it is safe, effective and has a low complication rate. (D'Afiero 2011 IUGA Pres 150; Khandwala 2011 AUGS Poster 143; Krofta 2011 IUGA Pres 116; 2011 Malinowski IUGA Pres 472; Singh 2011 ICS Abstract 575; Chen 2012 Chin J Obstet Gyn; DAfiero 2012 Int J Gynecol Obstet 19S3 Abs 0156; Hung Int Urogynecol J 2012; 23(Suppl 2):S202-203; Bezhenar 2013 - ICS Abs 765; Tsai Taiwan J Obstet Gynecol. 2014; 53(3):337-42). These data show a positive effect on sexual dysfunction and dyspareunia and a rate of mesh exposure that is generally less than 10%.

The largest of these studies, Singh 2011, was conducted in 116 women and at 12 months showed 92.2% anatomic success, significant improvements in patients' quality of life (PFDI-20,  $p < 0.001$ ), and a mesh exposure rate of 2.6%. There was statistically significant improvement in sexual function compared to baseline (PISQ-12,  $p = 0.008$ ). This is consistent with other Prosima data. For example, in the second largest cohort of 94 patients reported by Khandwala, mesh exposure was found in 5.3% ( $n=5$ ) of patients. 2 resolved after partial excision, 1 resolved with estrogen, and 2 cases ongoing episodes.

Dyspareunia was present at baseline in 8 of 35 (22.9%) sexually active patients and after surgery four of the eight (50%) had resolution. There were two patients (7.4%) who developed de novo dyspareunia out of the 27 who were sexually active without dyspareunia at baseline.

Similarly, Tsai 2014 reported that while baseline dyspareunia was 36.4% (8/22 patients), it dropped to 26.7% (4/15) after treatment with Prosima. Beheznar 2013 reported one case of dyspareunia, but the patient had dyspareunia at baseline. Sexual function by PISQ-12 scores statistically significantly improved. 41.1% of patients resumed sex and 5 patients (8.9%) started sexual intercourse after a long break (about 8 years), without any reported dyspareunia. Anatomic cure was 96% at 12 months. While there was a 14% mesh exposure rate, the patients still demonstrated statistically significant improvements in quality of life. The authors concluded that Prosima demonstrates success, both for anatomical and functional recovery of the pelvic organs, for safety because of the low invasiveness and a small amount of complications, satisfaction of the patients with the results of the treatment connected with the disappearance of the complaints related to violation of defecation, urination, as well as improved quality of life and the resumption of sexual activity. These data demonstrate that Prosima is safe, effective and is not defective.

The Ethicon IFU and Professional education materials properly identify the steps for using the Prosima device. The IFU and Professional Education materials for Prosima adequately and appropriately warns surgeons of the risks associated with the device. The

risks of Prosima were appropriately identified in the IFU, were taught in surgeons' education and training, and were widely publicized in peer-reviewed literature, at professional meetings, and in the FDA 2008 and 2011 Public Health Notices. The Professional Education and Ethicon sponsored Prosima study also identified potential risks and rates of complications. As noted above, these data were presented at conferences and also published in the peer reviewed literature, with peer reviewed papers being furnished to surgeons. Moreover, pain, erosion, scarring, contraction and dyspareunia and many other risks are warned of in the Ethicon IFU, Professional Education materials, Surgeon's Monographs, Patient Counseling materials, Patient Brochures, and other materials. Any specific warnings that may be identified by Plaintiff's experts either were not necessary or were adequately included in the Prosima IFU and accompanying materials mentioned above, as well as in the literature and professional education materials.

I hold all opinions to a reasonable degree of medical certainty and reserve the right to supplement my opinions based on new information and to respond to the depositions of plaintiffs' experts.

A handwritten signature in black ink, appearing to read 'C. Pramudji', written over a horizontal line.

Christina Pramudji, M.D.  
February 25, 2016

# Exhibit D

1                   IN THE UNITED STATES DISTRICT COURT  
2                   FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA  
3                   CHARLESTON DIVISION  
4       IN RE: ETHICON, INC.,           ) MASTER FILE NO.  
5       PELVIC REPAIR SYSTEM           ) 2:12-MD-02327  
6       PRODUCTS LIABILITY            )  
7       LITIGATION                    ) JOSEPH R. GOODWIN  
8       -----                        ) U.S. DISTRICT JUDGE  
9       THIS DOCUMENT RELATES TO )  
10      THE FOLLOWING CASES IN WAVE 1 OF MDL 200: )  
11      Joy Essman                    )  
12      Case No. 2:12-cv-00277        )  
13                                    )  
14      Barbara A. Hill               )  
15      Case No. 2:12-cv-00806        ) ORAL DEPOSITION OF  
16                                    ) CHRISTINA PRAMUDJI, M.D.  
17      Paula Kriz                    )  
18      Case No. 2:12-cv-00938        ) MARCH 24, 2016  
19                                    )  
20      Brenda Riddell                )  
21      Case No. 2:12-cv-00547        )  
22                                    )  
23      Sharon Carpenter              )  
24      Case No. 2:12-cv-00554        )  
25                                    )  
26      Mary Jane Olsen                )  
27      Case No. 2:12-cv-00470        )  
28                                    )  
29      Virginia White                 )  
30      Case No. 2:12-cv-00958        )  
31                                    )  
32      Sandra Wolfe                  )  
33      Case No. 2:12-cv-00335        )  
34                                    )  
35      Marie Smith (f/k/a Banks)     )  
36      Case No. 2:12-cv-01318        )  
37                                    )  
38      Sherry Fox                     )  
39      Case No. 2:12-cv-00878        )  
40                                    )  
41      Lois Durham                    )  
42      Case No. 2:12-cv-00760        )  
43                                    )  
44      Elizabeth Blynn Wilson        )  
45      Case No. 2:12-cv-01286        )  
46                                    )

1	Daphne Barker	)
	Case No. 2:12-cv-00899	)
2		)
	Wendy Hagans	)
3	Case No. 2:12-cv-00783	)
		)
4	Maria Eugenia Quijano	)
	Case No. 2:12-cv-00799	)
5		)
	Sharon Boggs	)
6	Case No. 2:12-cv-00368	)
		)
7	Robin Bridges	)
	Case No. 2:12-cv-00651	)
8		)
	Carey Cole	)
9	Case No. 2:12-cv-00483	)
		)
10	Cathy Warlick	)
	Case No. 2:12-cv-00276	)
11		)
	Donna Amsden	)
12	Case No. 2:12-cv-00960	)
		)
13	Heather Long	)
	Case No. 2:12-cv-01275	)
14		)
	Penny Rhynehart	)
15	Case No. 2:12-cv-01119	)
		)
16	Nancy Jo Williams	)
	Case No. 2:12-cv-00511	)
17		)
	Maria Stone	)
18	Case No. 2:12-cv-00652	)
		)
19	Teri Key Shively	)
	Case No. 2:12-cv-00379	)
20		)
	Charlene Logan Taylor	)
21	Case No. 2:12-cv-00376	)
		)
22	Tina Morrow	)
	Case No. 2:12-cv-00378	)
23		)
	Carol Jean Dimock	)
24	Case No. 2:12-cv-00401	)

1 Doctor, am I correct that you  
2 don't hold yourself out to be an expert with  
3 regard to the design of medical device kits  
4 for the treatment of prolapse?

5 A. I would say that I am somewhat  
6 of an expert in that area as far as being a  
7 user of the devices and also being involved  
8 in some of the labs that are held during the  
9 development of devices that I've been  
10 involved in. So as far as being asked to  
11 evaluate different devices as they're being  
12 produced, as far as that goes, I do have some  
13 expertise in that area.

14 Q. Well, let me see if I can ask  
15 it a different way. Am I correct that I  
16 would not expect you to offer design --  
17 strike that.

18 Am I correct that I would not  
19 expect you to offer opinions on the design of  
20 the Prosima?

21 MR. GAGE: Object to form.

22 A. My opinions would go to how I  
23 feel the design is based on use in my hands  
24 and based on the patient results. So I feel

1 very confident and familiar with evaluating  
2 the design based on those parameters.

3 BY MR. FAES:

4 Q. Is that the extent of the  
5 opinions that I would expect you to offer on  
6 the Prosima -- on the design of the Prosima,  
7 rather?

8 MR. GAGE: Object to form.

9 A. I may have some other opinions  
10 as far as they go to the mesh in general or  
11 pelvic floor kits or surgery in general.

12 BY MR. FAES:

13 Q. So you would have opinions on  
14 the design of the mesh in general or the  
15 design of pelvic floor kits and surgery in  
16 general?

17 A. Yes.

18 Q. Would those opinions on the  
19 design go beyond how those devices -- you  
20 believe those devices worked in your hands?

21 A. Yes, they potentially could.

22 Q. Well, you understand, Doctor,  
23 that this is my opportunity here today to  
24 learn what your opinions in this case might

1 be. What other opinions might you offer on  
2 the design of the Prosima or mesh kits or  
3 mesh in general?

4 A. Well, opinions about the design  
5 of the mesh in general, the way that the mesh  
6 is configured, the size of the pores, the  
7 materials that the mesh is made of. Or with  
8 the kits, how they're designed, how they --  
9 the development of the kits, the nuances of  
10 the trocars and how it worked in patients.

11 Q. Have you ever worked on the  
12 design team for a medical device?

13 A. No, only on a consulting basis.

14 Q. Am I correct in that you're not  
15 a biomedical engineer?

16 A. I'm not a biomedical engineer.  
17 I studied it, but I'm not a biomedical  
18 engineer.

19 Q. Do you hold yourself out as an  
20 expert in biomedical engineering?

21 A. To the degree that it applies  
22 to my practice, yes.

23 Q. Do you know what a design  
24 failure modes analysis is?

1           A.       I don't -- I'm not familiar  
2       with that term.

3           Q.       Is it fair to say that you have  
4       never reviewed any design failure mode  
5       analysis with respect to the Prosima,  
6       Gynemesh PS or Prolift?

7           A.       I may have, because just  
8       breaking down that terminology, I don't -- I  
9       can't give you a quick definition. But just  
10      breaking it down, it sounds like it's just  
11      testing the failure of the design with  
12      some -- probably some mechanical stretching  
13      or that sort of thing, but that's my  
14      conjecture. So I may have read about that.

15          Q.       Do you know what a process  
16      failure modes effects analysis is?

17          A.       I'm not familiar with that  
18      term.

19          Q.       Do you recall if you reviewed  
20      any process failure modes effects analysis  
21      with the Prosima, Prolift or Gynemesh PS  
22      devices?

23          A.       I'm not sure.

24          Q.       Do you know what an

1 applications failure modes effects analysis  
2 is?

3 A. I'm not sure.

4 Q. Do you recall if you've  
5 reviewed any of those for the Gynemesh PS,  
6 Prolift or Prosima device?

7 A. I'm not sure.

8 Q. Do you hold yourself out as  
9 having expertise or specialized knowledge  
10 regarding the type of mesh used in the  
11 Prosima, Prolift -- I guess I'll say  
12 Gynemesh PS device even though the mesh --  
13 that's the only thing in the Gynemesh PS  
14 device is the mesh?

15 A. Could you repeat the first part  
16 of the question?

17 Q. Yeah, I'll re-ask it because I  
18 didn't think it through before I asked it.

19 Am I correct in that you don't  
20 hold yourself out as having expertise or  
21 specialized knowledge regarding the type of  
22 mesh used in the Prosima or Prolift device?

23 MR. GAGE: Object to form.

24 A. No, that's incorrect because I

1       when the Gynemesh PS was cut with scissors  
2       and that those particles could become lodged  
3       in a woman's vaginal tissues and cause  
4       potential complications, do you believe those  
5       physicians' fears are unfounded?

6                       MR. GAGE: Object to form.

7               A.       Absolutely.

8       BY MR. FAES:

9               Q.       Doctor, are you going to  
10       offer -- do you plan to offer an opinion in  
11       this case about your personal success rate  
12       with the Prosima, Prolift or Gynemesh  
13       products?

14              A.       Yes.

15              Q.       What is the opinion you intend  
16       to offer about your personal success rate  
17       with those products?

18              A.       What I found is that the  
19       products were very successful with a high  
20       patient satisfaction with few complications.

21              Q.       Do you intend to offer a  
22       numeric success rate --

23              A.       No, I don't have a --

24              Q.       -- in conjunction with those

1 products?

2 A. No, I don't have a calculated  
3 numeric rate for my patients.

4 Q. Same question with regard to  
5 complication or erosion or extrusion rates,  
6 do you intend to offer an opinion in this  
7 case with regard to a numeric percentage of  
8 complications or erosions or extrusion rates  
9 that you've experienced personally?

10 A. Perhaps. I have in the past  
11 calculated reoperation rates, but I can't  
12 recall right now if it was on Prolift or on  
13 TVT. I would have to go back and look at my  
14 operative logs.

15 Q. So --

16 A. So I may have that rate on --

17 Q. Just reoperation rates?

18 A. Correct, just reoperation  
19 rates.

20 Q. Not exposure or extrusion  
21 rates?

22 A. Correct.

23 Q. Can you tell me how you arrived  
24 at those reoperation rates?

1           A.       I took my total number of  
2       reoperations and my total number of cases and  
3       just divided it.

4           Q.       And what --

5           A.       So it's a rough number.

6           Q.       And what is the numerator and  
7       denominator for those?

8           A.       I don't recall, as I sit here  
9       right now. I would have to look at it.

10          Q.       And who did -- who did the  
11       review?

12          A.       Myself.

13          Q.       Is there any documentation  
14       regarding the review or your findings that  
15       you used to come up with those rates?

16          A.       I have an operative log that I  
17       keep.

18          Q.       Do you know if that's been  
19       produced to us in this litigation?

20          A.       No, I don't believe so.

21                   MR. FAES: We would ask that  
22       that would be produced if the doctor  
23       is going to offer any opinions about  
24       her reoperation rates at trial.

1 MR. GAGE: I'll consult with  
2 her and let you know what our position  
3 is on that.

4 BY MR. FAES:

5 Q. Did you do any kind of analysis  
6 of patients that were lost to follow-up?

7 A. No, I did not.

8 Q. What time frame were you using  
9 for your reoperation rates to come up with  
10 your reoperation rate number for Prolift and  
11 Prosima?

12 A. Well, I just -- just from  
13 the -- when I started using the products  
14 until I did the analysis, however many years  
15 that was. I can't remember when I did that  
16 analysis.

17 Q. But you can't state a specific  
18 year that you started and stopped?

19 A. No, I can't remember right now.

20 Q. But it's fair to say it would  
21 go back to when you were working in Dallas in  
22 Dr. Anhalt's practice, correct?

23 A. Well, yeah. It wasn't in  
24 Dallas. It was here in Houston. But, yes,

1 back to 2005, when I started doing the  
2 Prolift, until I did the analysis, because  
3 there may have been some complications that  
4 were treated after I stopped using the  
5 products. But I can't remember when I did  
6 that.

7 Q. And if a doctor [sic] needed a  
8 reoperation and went to a different doctor  
9 other than you, you wouldn't have that  
10 information unless the patient shared it with  
11 you, correct?

12 A. That's correct.

13 Q. So your reoperation rates that  
14 you calculated would exclude any patients  
15 that went to other doctors for reoperation  
16 that you didn't know about, correct?

17 A. Yes. But kind of what I did in  
18 reverse, which this is very rough, but I  
19 included patients that came from other  
20 doctors in my reoperation rate. So some  
21 patients were not my original -- I was not  
22 the original implanter. So it's kind of --  
23 it's a very rough analysis. There's just  
24 sort of, okay, I did this many implants; how

1 many reoperations did I do? And this is  
2 just -- this isn't even -- this is just like  
3 a mesh exposure, mesh explant-type  
4 reoperation. It's not comprehensive.

5 Q. Okay. I think you've answered  
6 my question on that.

7 I hate to do this to you, but  
8 since there's no invoices yet on your  
9 case-specific depositions that you're going  
10 to be offering opinions on, I need to go  
11 through and ask you if you have a rough  
12 estimate of the number of hours you've spent  
13 on each of your cases. Do you know  
14 approximately how many hours you've spent on  
15 the Sharon Carpenter case?

16 MR. GAGE: Let me just say, I  
17 assume that by doing this that the  
18 individual lawyers will not ask the  
19 question and that you would agree as  
20 liaison counsel that I can say "asked  
21 and answered," we don't have to do it  
22 during the individual cases?

23 MR. FAES: Well, they might ask  
24 more specific questions, like break

# Exhibit E

Christina K. Pramudji, M.D.

1 IN THE UNITED STATES DISTRICT COURT  
2 SOUTHERN DISTRICT OF WEST VIRGINIA  
3 CHARLESTON DIVISION  
4 - - -

5 IN RE: ETHICON, INC., PELVIC : MASTER FILE NO.  
6 REPAIR SYSTEM PRODUCTS :: 2:12-MD-02327  
7 LIABILITY LITIGATION :  
8 : NO. 2327  
9 THIS DOCUMENT RELATES TO: : CASE NO.  
10 DIANNE M. BELLEW, :: 2:13-CV-22473  
11 - - -

12 September 17, 2014  
13 - - -

14 Videotaped deposition of CHRISTINA K. PRAMUDJI,  
15 M.D., taken pursuant to notice, was held at the Westin  
16 Galleria, 5060 West Alabama, Street, Houston, Texas, beginning  
17 at 10:24 a.m., on the above date, before Mary Kay Hendricks,  
18 CSR, a Registered Professional Reporter, Certified Shorthand  
19 Reporter.  
20 - - -

21 GOLKOW TECHNOLOGIES, INC.  
22 877.370.3377 ph|917.951.5672 fax  
23 deps@golkow.com  
24  
25

Christina K. Pramudji, M.D.

1           A. No, I wouldn't say that I would hold myself out  
2 as a design expert.

3           Q. You do not hold yourself out as a regulatory  
4 expert, correct?

5           A. That's correct.

6           Q. You do not hold yourself out as having any  
7 expertise or knowledge regarding what FDA regulations  
8 require to be included in the warnings and information  
9 provided by a medical device manufacturer for a product  
10 like the Prolift, do you?

11                   MR. SNELL: Form.

12           A. I know kind of what happened with Prolift, but  
13 I -- I would not say I'm an expert in that, no.

14           Q. (BY MR. SLATER) When you say you know what  
15 happened with Prolift, are you talking about the fact  
16 that it was withdrawn from the market?

17           A. No, no.

18                   MR. SNELL: Form.

19           A. I'm talking about the -- the fact that they  
20 followed the pathway for approval rather than going for  
21 the 510(k).

22           Q. (BY MR. SLATER) I didn't ask about that  
23 though. You realize that wasn't my question, right?

24           A. That's how I interpreted your question.

25           Q. You're not familiar with the regulations from

Christina K. Pramudji, M.D.

1 the FDA that specify what type of information is  
2 supposed to be found in warnings for the products like  
3 the Prolift, correct?

4 MR. SNELL: Form.

5 A. No, I'm not.

6 Q. (BY MR. SLATER) You're not familiar with the  
7 internal standards at Ethicon that the medical affairs  
8 and regulatory affairs people followed in terms of what  
9 information needed to be in the IFU and the patient  
10 brochure and other documents about the Prolift, correct?

11 A. That's correct. I don't know that.

12 Q. In drawing (sic) your opinions, you did not  
13 rely on any internal standards or any deposition  
14 testimony by any Ethicon witness as to what information  
15 needed to be in the IFU, the patient brochure or any  
16 other document about the Prolift, correct?

17 MR. SNELL: Form.

18 A. I don't -- I don't believe I did, not that I  
19 can recall off the top of my head, no.

20 Q. (BY MR. SLATER) You do not know what the  
21 requirements were that Ethicon had to satisfy before  
22 they could market the Prolift, do you?

23 A. No, I don't.

24 Q. You do not know what was considered by the  
25 Ethicon medical affairs director at the time that she

Christina K. Pramudji, M.D.

1 signed off to allow the Prolift to be marketed, do you?

2 A. No, I don't.

3 Q. You do not know what information was available  
4 to the Ethicon medical affairs director at the time that  
5 she signed off to allow the Prolift to be marketed, do  
6 you?

7 A. No, I don't.

8 Q. You do not know what information -- well, do  
9 you know what a DDSA or an FMEA is?

10 A. No clue.

11 Q. You don't know anything about the design  
12 control process where the DDSA and FMEAs were conducted,  
13 do you?

14 A. No.

15 Q. You know nothing about the risk assessment  
16 process and the post-market surveillance process at  
17 Ethicon regarding the Prolift, correct?

18 MR. SNELL: Form.

19 A. I know that they track phone calls coming in  
20 from physicians and patients, et cetera, but beyond that  
21 I don't -- I don't have any other detailed knowledge.

22 Q. (BY MR. SLATER) You have no information as to  
23 what type of information was provided to Ethicon  
24 specifically regarding the Prolift once the Prolift went  
25 on the market, correct?

Christina K. Pramudji, M.D.

1           A. I know that physicians would call in and  
2 patients would call in, but I'm not sure what you're  
3 referring to beyond that.

4           Q. You know that Ethicon would receive information  
5 about the Prolift from doctors and patients and others,  
6 but you have no specifics about what that information  
7 was, correct?

8           A. I mean, I've seen a few things, but -- I mean,  
9 not -- I don't have the whole body of that, no. I  
10 don't -- that would be beyond what I'm doing here.

11          Q. Did you ask the attorneys who retained you to  
12 make sure you had any documents that demonstrated  
13 Ethicon's knowledge as to severe or catastrophic  
14 complications with the Prolift? Did you ask to see that  
15 so you'd have a full picture of what Ethicon knew about  
16 the most serious complications?

17                   MR. SNELL: Form.

18          A. No, I did not.

19          Q. (BY MR. SLATER) Did you make any effort to  
20 learn that information?

21          A. No, I did not.

22          Q. In drawing your opinions, did you assume that  
23 if Ethicon knew about a severe complication with --  
24 connected with the Prolift that it would have been  
25 reported to the FDA?

Christina K. Pramudji, M.D.

1 A. Can you repeat that question, please?

2 Q. Sure. Did you assume that if Ethicon had  
3 knowledge of a severe complication occurring with the  
4 Prolift that it would have been reported to the FDA?

5 A. I never -- I never really thought about it.

6 Q. You gave no consideration to whether or not  
7 Ethicon evaluated or reported complications or reports  
8 of complications with the Prolift, correct?

9 A. That's correct.

10 MR. SNELL: Form.

11 Q. (BY MR. SLATER) Is it fair to say your  
12 opinions are based upon your own clinical experience and  
13 knowledge and are not with regard in any way to what  
14 Ethicon knew or what Ethicon specifically did? Is that  
15 fair?

16 MR. SNELL: Form.

17 A. Can you repeat that question one more time,  
18 please?

19 MR. SLATER: Let the court reporter read it  
20 back just to get it the same way.

21 (The requested material  
22 was read by the reporter.)

23 A. I'm not sure how to answer that because I -- I  
24 mean, I have some information about that, but I don't  
25 have -- you know, that wasn't the main focus, but I do

Christina K. Pramudji, M.D.

1 information.

2 Q. (BY MR. SLATER) If you cited an article in  
3 your report, did you attempt to be -- I'm going to use  
4 the term "fair and balanced" in summarizing the data  
5 from the report -- from the study if you actually gave  
6 data from the study in your report?

7 A. Yes, I did.

8 Q. Did you feel that was your obligation as an  
9 expert to give both sides of the story to the extent  
10 both sides are told in an article?

11 A. Yes.

12 Q. If you failed to do so, that would be a failure  
13 in being objective, correct?

14 MR. SNELL: Form.

15 A. Yes.

16 Q. (BY MR. SLATER) In forming your opinions as to  
17 whether or not the warnings for the Prolift were  
18 adequate to communicate the risks and complications, you  
19 did not refer to or rely on any specific standard,  
20 correct?

21 A. I mean, I relied on general surgical principles  
22 and standards.

23 Q. Well, in determining whether or not the IFU for  
24 the Prolift adequately warned of the risks and  
25 complications, did you base your opinion on your own

Christina K. Pramudji, M.D.

1 judgment and your own evaluation based on your  
2 experience?

3 A. Yes.

4 Q. You did not rely on any particular standards,  
5 for example, an FDA regulation or any statement by  
6 anyone at Ethicon as to what they were supposed to  
7 communicate in those warnings, correct?

8 A. Correct.

9 MR. SNELL: Form.

10 Q. (BY MR. SLATER) You could not give me an  
11 objective standard that you applied. It was simply --  
12 and then I could then apply your same standard. It's  
13 simply what you think is right or adequate based on your  
14 own experience, right?

15 MR. SNELL: Form.

16 A. Yeah. I would say that's correct.

17 Q. (BY MR. SLATER) Okay. If Ethicon knew of  
18 significant risks and complications with the Prolift  
19 from their own internal studies or from information they  
20 got from other physicians, would you agree they needed  
21 to warn of that information in the IFU?

22 A. No, not necessarily.

23 Q. Do you know if Ethicon internally thought that  
24 they needed to warn based on the standards that they say  
25 that -- rephrase. Do you know whether the standards

# Exhibit F

Confidential - Subject to Stipulation and Oder of Confidentiality

1 - - -  
2  
3 IN RE: :SUPERIOR COURT OF  
4 PELVIC MESH/GYNECARE :NEW JERSEY  
5 LITIGATION :LAW DIVISION -  
6 :ATLANTIC COUNTY  
7 :  
8 :MASTER CASE 6341-10  
9 :  
10 :CASE NO. 291 CT

11  
12 CONFIDENTIAL-SUBJECT TO STIPULATION AND ORDER OF  
13 CONFIDENTIALITY  
14 - - -

15  
16 September 12, 2012  
17  
18 - - -

19  
20 Volume I of the transcript of the  
21 Deposition of CHARLOTTE OWENS, M.D., called for  
22 Videotaped Examination in the above-captioned  
23 matter, said deposition taken pursuant to  
24 Superior Court Rules of Practice and Procedure,  
25 by and before JoRita B. Meyer, a Certified  
Realtime Reporter, Registered Merit Reporter,  
and Certified Court Reporter for the State of  
Georgia, at the offices of Troutman Sanders,  
600 Peachtree Street Northeast, Atlanta,  
Georgia, commencing at 9:39 a.m.

26 - - -  
27 GOLKOW TECHNOLOGIES, INC.  
28 877.370.3377 ph|917.951.5672 fax  
29 deps@golkow.com

Confidential - Subject to Stipulation and Oder of Confidentiality

1 purpose of the IFU?

2 A. The IFU is a document to provide some  
3 general and some specific information to the  
4 physician about the use of our product.

5 Q. Did you understand that the IFU is  
6 considered under FDA regulations to be the  
7 primary label for the medical device, in this  
8 case, the PROLIFT?

9 A. Yes.

10 Q. And you understood this would be the  
11 primary source of information that surgeons  
12 would look to to get information with regard to  
13 the safety and efficacy and potential risks of  
14 using the PROLIFT with patients, correct?

15 A. When you say "primary," what do you  
16 mean by "primary"?

17 Q. Meaning this would be the first --  
18 well, rephrase.

19 When I say "primary," I say that  
20 if -- if there was anything that a surgeon  
21 would look at, it would be this, this would be  
22 the first thing that they would look to?

23 A. I don't know if it's the first thing  
24 that they would look to, because this would  
25 have been part of our entire professional

Confidential - Subject to Stipulation and Oder of Confidentiality

1 education package; so this would be one of the  
2 things that they would look to, yes.

3 Q. Do you understand the significance  
4 under FDA regulations of the IFU being the  
5 primary label for the PROLIFT?

6 A. I understand the FDA regulations  
7 around the document. I also understand the way  
8 that physicians are trained and operate.

9 MR. SLATER: Move to strike from "I  
10 also" forward.

11 BY MR. SLATER:

12 Q. What's your understanding as to the  
13 significance of the IFU being the primary label  
14 for the PROLIFT from FDA regulatory standpoint?

15 A. That the agency sees this as the  
16 document that they review as a part of the  
17 packaging for our materials. So it should  
18 contain the relevant indications, description,  
19 and -- and other pertinent information as  
20 prescribed by the regulations.

21 Q. That would also include all necessary  
22 contraindications, warnings and precautions,  
23 and adverse reactions, correct?

24 A. It would include warnings,  
25 precautions, contraindications, adverse

Confidential - Subject to Stipulation and Order of Confidentiality

1 reactions, sterility, disposal, storage,  
2 et cetera.

3 Q. You have understood that all of the  
4 information in the IFU needed to be accurate,  
5 correct?

6 A. Yes.

7 Q. You understood that physicians were  
8 going to rely on the IFU in making decisions  
9 about whether or not to use the PROLIFT in  
10 treating patients, correct?

11 MR. BROWN: Objection.

12 THE WITNESS: Physicians will not  
13 rely solely on the IFU for making their  
14 decisions. Physicians will use the IFU  
15 to help inform them, but they will also  
16 use other information.

17 BY MR. SLATER:

18 Q. You understood physicians would rely,  
19 at least in part, on the PROLIFT IFU in making  
20 decisions about whether they wanted to use that  
21 product, that medical device, that system, in  
22 their patients, correct?

23 MR. BROWN: Objection.

24 THE WITNESS: Physicians will use  
25 this document and other documents to

Confidential - Subject to Stipulation and Oder of Confidentiality

1           decide if they want to learn more about  
2           the system, and ultimately will use  
3           their training, education, and  
4           experience, plus this document, to  
5           decide if they want to use it.

6       BY MR. SLATER:

7           Q.    Did you understand that it was  
8           necessary to clearly and unambiguously  
9           communicate all necessary contraindications,  
10          warnings and precautions, and adverse reactions  
11          to physicians through the IFU?

12          A.    I understand the document should be  
13          clear and unambiguous, yes.

14          Q.    Did you understand that it was  
15          necessary for Gynecare, to the extent that a  
16          risk was understood to exist with the PROLIFT,  
17          to communicate it in the IFU as opposed to  
18          assuming that surgeons would figure out that  
19          risk on their own?

20          A.    I don't think you're giving surgeons  
21          enough credit. Surgeons don't have to figure  
22          out the complications of an area that they  
23          operate. Surgeons are trained to know the  
24          complications of the area in which they  
25          operate.

Confidential - Subject to Stipulation and Order of Confidentiality

1 BY MR. SLATER:

2 Q. Does it mean too much tension?

3 A. It's not that simple.

4 Q. How would a surgeon doing the  
5 procedure be able to objectively verify, based  
6 on an objective standard, that they had placed  
7 or not placed the mesh with excessive tension?

8 A. They would be able to look at the  
9 repair after surgery and see if it looks  
10 relaxed or see if it looks like it's under  
11 tension.

12 Q. So that's how they would do it?

13 A. That's generally how it was done.

14 Q. Did you ever perform the PROLIFT  
15 procedure?

16 A. On the cadavers, yes. In live  
17 people, because I was not practicing during my  
18 tenure at Ethicon, no.

19 Q. Did you ever on your own, without any  
20 other surgeon performing the procedure -- did  
21 you ever place Gynemesh in a human's body?

22 A. No.

23 Q. Look at the adverse reactions,  
24 please. It was your understanding that you  
25 needed to list each of the adverse reactions

Confidential - Subject to Stipulation and Order of Confidentiality

1       that were known to you in Medical Affairs in  
2       this section, correct?

3             A.     Yes.

4             Q.     And you understood that if you failed  
5       to list adverse reactions that you were aware  
6       of, that that would render that warning  
7       deficient to some extent, correct?

8             A.     Deficient?

9             MR. BROWN:  Objection.

10            THE WITNESS:  I would say that we  
11       listed the adverse reactions that we  
12       knew were adequate and sufficient for  
13       this document.

14    BY MR. SLATER:

15            Q.     Well, you just said a moment ago you  
16       agreed with me that you understood you were  
17       supposed to list each of the adverse reactions  
18       that you in Medical Affairs knew existed at the  
19       time of launch, correct?

20            A.     We listed the adverse events that we  
21       knew to be directly related to the information  
22       that we had at this time.

23            Q.     Okay.  Were there risks -- well,  
24       rephrase.

25                    You see where it says, at the end of

1 A. Correct.

2 Q. And it says the potential effect of  
3 that is damage to the cannula and the potential  
4 hazard what could occur would be tissue damage,  
5 correct?

6 A. Correct.

7 Q. And the potential harm that could  
8 result here is described as bleeding, correct?

9 A. Correct.

10 Q. And you understood that through your  
11 review of this -- rephrase.

12 And you understood that it was  
13 required that you capture all of the different  
14 failure modes, all the things that could go  
15 wrong in the procedure, even if the doctor was  
16 properly trained and following the proper  
17 procedure, and the effects of those failure  
18 modes, the hazards that could occur, and the  
19 resulting harms, and you were supposed to  
20 capture all of them, correct?

21 A. Yes, all that we could conceive of,  
22 yes.

23 Q. Now, one of the things that could  
24 happen is during the passage of the guides, is  
25 the pudendal nerve could be injured, correct?

1 specifically mentioned in the document.

2 BY MR. SLATER:

3 Q. And therefore, none of them are  
4 specifically scored, correct?

5 A. They would have been included in  
6 things other than the terms that you mentioned.

7 Q. As the document appears and as it was  
8 specifically and carefully written by quality  
9 engineering, with your approval, those items do  
10 not appear and are not specifically scored,  
11 correct?

12 A. Those items are not specifically  
13 mentioned, no.

14 Q. All right. Now let's look at the  
15 dFMEA, which is Exhibit 629. You understood  
16 the purpose of the dFMEA, correct?

17 A. Yes.

18 Q. That's the Design Failure Modes and  
19 Effects Analysis, correct?

20 A. Yes.

21 Q. And what was the purpose of this  
22 analysis?

23 A. To review the potential risk  
24 associated with the design of the product.

25 Q. And when you say "associated with the

1 design of the product," that means that when  
2 the product is in a woman's body and the  
3 product was manufactured completely consistent  
4 with the specifications, these are the things  
5 that could go wrong and harm a patient,  
6 correct?

7 A. Correct.

8 Q. Let's look now at this dFMEA, and  
9 let's look at page -- looking at the Bates  
10 number 03573, the actual chart and grid.

11 And it indicates that you were one of  
12 the individuals who provided input as medical  
13 director, correct?

14 A. Yes.

15 Q. And again, as with the aFMEA, you had  
16 to sign off on the dFMEA in order for this gate  
17 to be surpassed so the product could move  
18 closer to Product Release Authorization and to  
19 be marketed to be put in women's bodies,  
20 correct?

21 A. Correct.

22 Q. And what this does is, in the chart,  
23 is the different components of the PROLIFT kit  
24 are each evaluated in terms of what harms they  
25 could cause if they were to fail, correct?

# Exhibit G

Confidential - Subject to Stipulation and Order of Confidentiality

1 - - -  
2 :SUPERIOR COURT OF  
:NEW JERSEY  
3 IN RE: :LAW DIVISION -  
PELVIC MESH/GYNECARE :ATLANTIC COUNTY  
4 LITIGATION :  
:MASTER CASE 6341-10  
5 :  
:CASE NO. 291 CT

6  
7 CONFIDENTIAL-SUBJECT TO STIPULATION AND ORDER OF  
8 CONFIDENTIALITY

- - -  
9 March 14, 2012  
- - -

10  
11 Transcript of the continued  
12 deposition of DAVID B. ROBINSON, MD, called for  
13 Videotaped Examination in the above-captioned  
14 matter, said deposition taken pursuant to Superior  
15 Court Rules of Practice and Procedure by and before  
16 Ann Marie Mitchell, a Federally Approved Certified  
17 Realtime Reporter, Registered Diplomate Reporter,  
18 Certified Court Reporter, and Notary Public for the  
19 State of New Jersey, at the offices of Riker Danzig  
20 Scherer Hyland & Perretti LLP, Headquarters Plaza,  
21 One Speedwell Avenue, Morristown, New Jersey,  
22 commencing at 9:35 a.m.

23 - - -  
GOLKOW TECHNOLOGIES, INC.  
24 877.370.3377 ph| 917.951.5672 fax  
deps@golkow.com  
25

Confidential - Subject to Stipulation and Order of Confidentiality

1           A.           Well, I don't know about believing  
2     it, but they need to read it and begin a discussion  
3     with their physicians. I can't --

4           Q.           Does it say anywhere in the patient  
5     brochure, in big, set-off letters so that the  
6     patient could not miss it, please understand, you're  
7     not expected to rely on this document. It's just  
8     supposed to be a jumping off point for your  
9     discussion with your physician? Is there anything  
10    like that?

11                   MR. GAGE: Objection.

12                   THE WITNESS: I can't recall, but I  
13    have to believe in there that there is language to  
14    say, discuss with your physician.

15                   MR. SLATER: Move to strike after "I  
16    can't recall."

17    BY MR. SLATER:

18           Q.           Did you expect patients to think that  
19    what was written in the Prolift® patient brochure  
20    was true?

21           A.           Yes.

22           Q.           Did you expect patients to rely on  
23    Ethicon to tell them the truth about the Prolift®  
24    procedure in the patient brochure that was dedicated  
25    to the Prolift®?

Confidential - Subject to Stipulation and Order of Confidentiality

1           A.           As best we knew at the time it was  
2     created, yes.

3           Q.           So Ethicon expected that when a  
4     patient would read the patient brochure, they would  
5     believe what they were reading. Right?

6           A.           Again, I can't speak for their  
7     belief, but I believe it should be a body of  
8     information that you then take to your doctor to  
9     talk about.

10                   MR. SLATER: Move to strike.

11     BY MR. SLATER:

12           Q.           You knew that there were patients who  
13     would read the patient brochure for the Prolift® and  
14     rely on Ethicon's statements to them about the  
15     benefits and risks of the procedure as part of their  
16     decision about whether or not to let a surgeon put a  
17     Prolift® in their body. Right?

18                   MR. GAGE: Objection.

19                   THE WITNESS: As part of that, yes.

20     BY MR. SLATER:

21           Q.           And nowhere in that patient brochure  
22     are patients told that they can suffer pain as a  
23     result of the Prolift®. Right?

24                   MR. GAGE: Objection.

25                   THE WITNESS: I'd have to look at the

Confidential - Subject to Stipulation and Order of Confidentiality

1 director in Ethicon, you did not expect physicians  
2 to rely upon the IFU for the Prolift® as an accurate  
3 disclosure of the risks associated with the Prolift®  
4 system?

5 MR. GAGE: Objection.

6 THE WITNESS: No. I think what I  
7 said is I didn't -- they shouldn't depend on it as  
8 the sole source of their information regarding the  
9 Prolift® system.

10 BY MR. SLATER:

11 Q. My question is this: Did you expect  
12 surgeons who were considering using the Prolift® to  
13 rely upon the Prolift® IFU to accurately disclose  
14 the risks associated with the use of the Prolift®  
15 system?

16 MR. GAGE: Objection.

17 THE WITNESS: We should accurately  
18 represent what we knew to be risks at the time, yes.

19 BY MR. SLATER:

20 Q. You knew that was required by federal  
21 law. Right?

22 MR. GAGE: Objection.

23 BY MR. SLATER:

24 Q. By the FDA. Right?

25 MR. GAGE: Objection.

Confidential - Subject to Stipulation and Order of Confidentiality

1 THE WITNESS: Actually, I don't know  
2 whether the FDA -- that is a regulatory decision.

3 BY MR. SLATER:

4 Q. And you felt that was your obligation  
5 to physicians so they would know what the potential  
6 adverse reactions were if they used that product.  
7 Right?

8 MR. GAGE: Objection.

9 THE WITNESS: To the best of our  
10 knowledge at the time, yes.

11 BY MR. SLATER:

12 Q. And if Ethicon had knowledge of an  
13 adverse reaction and did not include it in the  
14 Prolift® IFU, then the IFU would be deficient to  
15 that extent. Right?

16 MR. GAGE: Objection.

17 THE WITNESS: No, that's not true.

18 BY MR. SLATER:

19 Q. Okay.

20 A. Because --

21 Q. So let me understand this.

22 MR. GAGE: The witness would like to  
23 finish his answer.

24 MR. SLATER: He just said no. That's  
25 all I was asking.

Confidential - Subject to Stipulation and Order of Confidentiality

1           Q.       Well, I'm asking you, based on your  
2       participation in the process at Ethicon, would that  
3       be incorrect?

4                   MR. GAGE:   Objection.

5                   THE WITNESS:  I don't remember ever  
6       being asked to give the -- a final decision about  
7       adverse events being put in an IFU.

8       BY MR. SLATER:

9           Q.       Let me understand this.  Ethicon  
10       understood it was expected to put all of the adverse  
11       events into the IFU.  However, if Ethicon failed to  
12       list -- I'm going to ask the question differently.

13                   If Ethicon determined an adverse  
14       reaction to be material, meaning it doesn't just  
15       happen, you know, so infrequently that you don't  
16       have to consider it but it happens enough that you  
17       can actually put a percentage on it --

18           A.       Well --

19                   MR. GAGE:  Let him finish his  
20       question.

21       BY MR. SLATER:

22           Q.       Let me ask you this.

23                   How would you define a complication  
24       to be material enough that it would need to be  
25       listed in the IFU?  How did you define that as

Confidential - Subject to Stipulation and Order of Confidentiality

1 medical director?

2 A. Well, it would either need to have a  
3 frequency or a severity that had some implication  
4 for a risk/benefit ratio.

5 Q. Okay.

6 If a complication met that standard,  
7 it needed to be called out in the IFU. Right?

8 A. Yes.

9 Q. And if it was not -- rephrase.

10 And if a complication that met that  
11 standard was not included in the IFU, the IFU would  
12 be deficient by definition. Correct?

13 MR. GAGE: Objection.

14 THE WITNESS: I think it has to be  
15 based on the information you have at the time the  
16 IFU is created, so it will always evolve.

17 BY MR. SLATER:

18 Q. The information Ethicon had about the  
19 complications and risks from the Prolift® evolved  
20 over the years. Right?

21 A. Yes.

22 Q. That evolution was actually fairly  
23 significant as more and more procedures were done  
24 and Ethicon saw more clinical studies. Right?

25 MR. GAGE: Objection.

# Exhibit H

Confidential - Subject to Stipulation and Order of Confidentiality

1 - - -  
2 :SUPERIOR COURT OF  
:NEW JERSEY  
3 IN RE: :LAW DIVISION -  
PELVIC MESH/GYNECARE :ATLANTIC COUNTY  
4 LITIGATION :  
:MASTER CASE 6341-10  
5 :  
:CASE NO. 291 CT

6  
CONFIDENTIAL-SUBJECT TO STIPULATION AND ORDER OF  
7 CONFIDENTIALITY

8 - - -  
9 May 18, 2012

10 - - -  
11 Transcript of the deposition of  
12 SEAN M. O'BRYAN, called for Videotaped  
13 Examination in the above-captioned matter, said  
14 deposition taken pursuant to Superior Court Rules  
15 of Practice and Procedure by and before Maryellen  
16 Coughlin, a Certified Realtime Reporter,  
17 Registered Professional Reporter, and Notary  
18 Public for the Commonwealth of Massachusetts, at  
19 the offices of Campbell Campbell Edwards &  
20 Conroy, P.C., One Constitution Center, 3rd Floor,  
21 Boston, Massachusetts, commencing at 10:05 a.m.

22 - - -  
GOLKOW TECHNOLOGIES, INC.  
23 877.370.3377 ph | 917.951.5672 fax  
deps@golkow.com

Confidential - Subject to Stipulation and Order of Confidentiality

1 warnings that a patient could be faced with that  
2 are important for the patient.

3 Q. And to the extent you had input  
4 into the Prolift® IFU drafting process, you  
5 certainly wanted to make sure that any warnings  
6 of any significant potential risks would be  
7 explicitly communicated to the intended or  
8 foreseeable users of the Prolift®, correct?

9 MS. KABBASH: Objection.

10 A. Sure. I rely on the medical team  
11 to tell me what is significant and what is  
12 important to convey into the instructions for  
13 use, package insert.

14 Q. When you worked on that project, it  
15 was your understanding from an FDA regulatory  
16 perspective it would not be legitimate to not  
17 include warnings of potentially significant  
18 adverse events based on a decision that the  
19 surgeons would figure that out on their own?

20 MS. KABBASH: Objection.

21 A. No, that's correct.

22 Q. Would you turn to Page 22, please.  
23 It's Paragraph D, D.1.3. The question is asked,  
24 "Do the results of the design validation  
25 performed as a result of this change in materials

Confidential - Subject to Stipulation and Order of Confidentiality

1 A. Yes, yes.

2 Q. Do you know if those were done by  
3 the TVM or the Prolift® procedure or by other  
4 procedures?

5 A. I can't recall. I'm sorry.

6 Q. You were asked by counsel about  
7 whether or not it was your responsibility to make  
8 sure adverse events were properly communicated in  
9 the IFU, and I think you said your responsibility  
10 to make sure that once medical affairs decided  
11 that those adverse events belonged, were  
12 significant enough that they needed to be  
13 communicated because they were risks associated  
14 with the Prolift®, you want to make sure that it  
15 would not be presented in a confusing way,  
16 correct?

17 A. Yes.

18 Q. And part of that would be that if  
19 such a risk was known and was going -- rephrase.

20 And part of that would be that  
21 if -- rephrase.

22 This is the last question of the  
23 day. And part of that review that you're talking  
24 about would include making sure that, to the  
25 extent a risk did need to be included in the IFU,

Confidential - Subject to Stipulation and Order of Confidentiality

1       because, as you said, if it's known by medical  
2       affairs to be a risk connected to the Prolift® it  
3       should be in there, you don't want it to be  
4       presented in a confusing way, and you want it to  
5       be explicitly and clearly set forth, correct?

6                       MS. KABBASH: Objection.

7               A.       That's a fair assessment, yeah.

8                       MR. SLATER: No other questions.

9                       MS. KABBASH: I think we're done.

10                      THE VIDEOGRAPHER: Person on the  
11       phone any questions?

12                      This concludes the May 18th, 2012,  
13       deposition of Sean M. O'Bryan. The number of  
14       tapes used today was 3. We are off the record at  
15       4:59 p.m.

16                      (Deposition suspended/concluded  
17                      at 4:59 p.m.)

18

19

20

21

22

23

24

25

# Exhibit I

1                   IN THE UNITED STATES DISTRICT COURT  
2                   FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA  
3                   CHARLESTON DIVISION

4           IN RE: ETHICON, INC.,  
5           PELVIC REPAIR SYSTEMS  
6           PRODUCTS LIABILITY LITIGATION           MDL NO. 2327

---

7           Jo Huskey and Allen

8           Huskey,

9                   Plaintiffs,

10          v.

Case No. 2:12-cv-05201

11          Ethicon, Inc., et al.,

12                   Defendants.

13  
14                   ORAL DEPOSITION OF  
15                   CHRISTINA PRAMUDJI, M.D.  
16                   Friday, April 11, 2014

17  
18  
19  
20  
21                   GOLKOW TECHNOLOGIES, INC.  
22                   877.370.3377 ph|917.591.5672 fax  
23                   deps@golkow.com  
24

1 the removal surgeries can be significantly  
2 more complicated than the original  
3 implantation surgery for the TVT-O, right?

4 MR. SNELL: Form.

5 A. It can be harder to find the  
6 sling if it's not a dyed sling.

7 BY MS. KIRKPATRICK:

8 Q. And the removal surgery requires  
9 dissection of some of the pelvic tissue,  
10 correct?

11 A. Well, it requires dissecting  
12 around the urethra, primarily.

13 Q. And that can cause additional  
14 scar tissue, correct, simply because you're  
15 having more surgery in the same location?

16 A. It could, yes.

17 Q. Are there any other complications  
18 that you think are risks that come from the  
19 removal surgery itself?

20 A. No.

21 Q. So just the possibility of  
22 additional scarring?

23 A. Yes.

24 Q. Okay. We've been talking a lot

1 about kind of the procedure that's used here.

2 You're not a biomaterials expert, correct?

3 A. Well, I know about the materials  
4 that I use for surgery, so I would say that  
5 I -- you know, I'm knowledgeable about what I  
6 implant in patients.

7 Q. Okay. What's the Ethicon TVT-O  
8 sling made of?

9 A. Polypropylene.

10 Q. Okay. What's added to that  
11 polypropylene?

12 A. What's added to it?

13 Q. Uh-huh.

14 A. I don't know if anything's added  
15 to it.

16 Q. Do you know if there's any  
17 antioxidants used in it?

18 A. No, I don't know.

19 Q. Do you know what its molecular  
20 weight is?

21 A. I've seen it before, but I don't  
22 know off the top of my head.

23 Q. Do you know whether it's been  
24 oxidized before it's been placed into a

1 woman's body?

2 A. No.

3 Q. Do you know anything about the  
4 process of oxidation of polypropylene?

5 A. No.

6 Q. And that's not the type of  
7 information -- you know that it's made of  
8 polypropylene, but you're not intending to  
9 offer opinions here concerning the chemical  
10 processes that are involved with  
11 polypropylene, correct?

12 A. I don't know about the chemical  
13 processes.

14 Q. Okay. So you would defer -- you  
15 would defer to other experts who would be  
16 biomaterials experts or who would be  
17 specialists in polypropylene for that  
18 particular type of information?

19 MR. SNELL: Form.

20 A. I know how it -- I focus on it  
21 from the perspective of my patients.

22 BY MS. KIRKPATRICK:

23 Q. Okay. So you focus, though, on  
24 how you believe the polypropylene sling

1 performs in your patients, both from an  
2 efficacy standpoint, correct, and from  
3 complications that you see?

4 A. From my experience and from the  
5 vast body of literature that's available on  
6 polypropylene slings.

7 Q. Okay. But I guess I'm just  
8 trying to figure out what the parameters of  
9 your testimony are. You're not going to come  
10 in and you're not planning on holding  
11 yourself out as an expert on polymers and  
12 polypropylene and degradation or any of those  
13 particular issues related to polypropylene,  
14 are you?

15 MR. SNELL: Form. And I will say  
16 she is. I am putting her up on that, and  
17 it is in her report.

18 BY MS. KIRKPATRICK:

19 Q. Okay. How does polypropylene  
20 degrade?

21 A. It doesn't degrade.

22 Q. So your opinion, sitting here  
23 today, that there is no way that any  
24 polypropylene that exists in this world can

1 degrade?

2 MR. SNELL: That's overbroad,  
3 form.

4 Go ahead.

5 A. That's a very broad question.  
6 You know, from how it's used in the body in  
7 sutures and in slings, it doesn't degrade;  
8 that's why it's a permanent suture. That's  
9 why heart surgeons rely on it and cardiac  
10 surgeons rely on it to sew up your aorta when  
11 you have aortic surgery.

12 So if it degraded, it would not  
13 be used in that application. There's no  
14 clinical degradation that occurs.

15 BY MS. KIRKPATRICK:

16 Q. So you believe that there's no  
17 evidence that exists, either in Ethicon's own  
18 documents or in the literature, that supports  
19 the theory that polypropylene sutures can  
20 degrade --

21 MR. SNELL: Form.

22 Go ahead.

23 BY MS. KIRKPATRICK:

24 Q. -- in vivo?

1 MR. SNELL: Form.

2 A. I mean, I can't say that there's  
3 nothing out there that they didn't do any  
4 kind of manipulation to polypropylene or look  
5 at it a certain way and found some  
6 degradation there, but does it matter to  
7 patients and to this case, no.

8 BY MS. KIRKPATRICK:

9 Q. Has Mr. Snell or any of the  
10 attorneys for Ethicon provided you with any  
11 Ethicon documents reflecting degradation of  
12 polypropylene sutures?

13 A. I mean, I think I saw some  
14 internal communication, I can't remember if  
15 it was from Mr. Kountze or from Mr. Snell, I  
16 don't remember, but I know that that is out  
17 there, that that was something that the  
18 engineers were talking about and Ethicon was  
19 talking about.

20 But clinically, I'm telling you  
21 it does not make a difference, and I don't  
22 believe that there's degradation that occurs  
23 that it makes any hill of beans' difference  
24 for patients.

1 Q. Okay. So let me just figure out  
2 what you are testifying about and what you're  
3 not testifying about. You don't have a basis  
4 for saying whether polypropylene does or  
5 doesn't degrade.

6 What you are here to offer your  
7 opinion on is that regardless of whether  
8 polypropylene degrades or doesn't degrade,  
9 there's no clinical significance to a  
10 particular patient?

11 A. I don't think it degrades.

12 MR. SNELL: Hold on, hold on,  
13 hold on. Form. That misstates, too.

14 Go ahead.

15 A. I don't think it degrades and I  
16 think there's other evidence that shows that  
17 it doesn't degrade.

18 BY MS. KIRKPATRICK:

19 Q. Have you asked Ethicon, in  
20 reaching that opinion, to provide you with  
21 all of the information that they have  
22 concerning the potential degradation of  
23 polypropylene sutures?

24 A. No.